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APPLICATION NUMBER: *60/612,009*
FILING DATE: *September 22, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US05/10005*

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CERTIFICATE OF MAILING

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Beatrice M. Aveline, Ph.D.

PROVISIONAL APPLICATION TRANSMITTAL

(REQUEST FOR FILING A PROVISIONAL APPLICATION FOR PATENT UNDER 37 CFR 1.53(C))

Dear Sir:

Please find enclosed a provisional patent application and papers as follows for:

Inventor(s):

Given Name (first)	Middle Initial	Family Name or Surname	Residence
John	A	Porco	Chestnut, MA
Baudouin		Gerard	Allston, MA
Guilford		Jones	Canton, MA

Title of the Invention: Synthesis of Rocaglamide Natural Products via Photochemical Generation of Oxidopyrylium Species

A) ENCLOSED APPLICATION PARTS:

1) X Specification, consisting of: PAGES 61

a) X Description (30 pages)

b) X Claims (8 pages)

c) X Abstract (1 page)

d) X Drawing(s) (22 Sheets)

B) OTHER ACCOMPANYING APPLICATION PARTS:

1) X Return Receipt Postcard (MPEP § 503) (specifically itemized)

2) ___ Application Data Sheet. See 37 CFR 1.76

3) ___ **OTHER:** (if applicable, specified below)

C) CORRESPONDENCE ADDRESS:

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D) METHOD OF PAYMENT OF FILING FEES:

__ Applicant claims small entity status. See 37 CFR §1.27.

___ Statement Verifying Small Entity Status (optional)

X A check or money order is enclosed to cover the filing fees.

X The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 03-1721.

FILING FEE AMOUNT ($): 80.00.

E) GOVERNMENT SUPPORT

THE INVENTION WAS MADE BY AN AGENCY OF THE UNITED STATES GOVERNMENT OR UNDER A CONTRACT WITH AN AGENCY OF THE UNITED STATES GOVERNMENT:

X NO.

___ YES

Respectfully Submitted,

Dated: September 22, 2004

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Synthesis of Rocaglamide Natural Products *via* Photochemical Generation of Oxidopyrylium Species

Related Patent Applications

[1] Part of the invention described in the present patent application has been disclosed in a Provisional Patent Application (U.S.S.N. 60/555,448), which was filed on March 23, 2004. The Provisional Application filed last March is incorporated herein by reference in its entirety.

Background of the Invention

[2] The plant genus *Aglaia* native of the tropical rain forests of Indonesia and Malaysia is the source of a unique group of densely functionalized natural products presented on Figure 1 (P. Proksch *et al.*, Curr. Org. Chem., 2001, 5: 923-938). The rocaglamides, including the parent molecule (compound **1**; M.L. King *et al.*, J. Chem. Soc., Chem. Commun., 1982, 1150-1151) and the recently isolated dioxanyloxy-modified derivative silvestrol (compound **2**; B.Y. Hwang *et al.*, J. Org. Chem., 2004, 69: 3350-3358), possess the cyclopenta[*b*]tetrahydrobenzofuran ring system (presented in red on Fig. 1). The structurally related aglains (*e.g.*, compounds **3** and **4**), which contain a cyclopenta[*bc*]benzopyran structure (in blue on Fig. 1), have also been isolated from *Aglaia* (V. Dumontet *et al.*, Tetrahedron, 1996, 52: 6931-6942). The forbaglins (*e.g.*, compound **5**) are benzo[*b*]oxepines (in green on Fig. 1) derived from formal oxidative cleavage of the aglain core.

[3] The rocaglamides exhibit potent anticancer (M.L. King *et al.*, J. Chem. Soc., Chem. Commun., 1982, 1150-1151) and antileukemic activity (S.K. Lee *et al.*, Chem. Biol. Interact., 1998, 115: 215-228), as well as NF-κB inhibitory activity at nanomolar concentrations in human T cells (B. Baumann *et al.*, J. Biol. Chem., 2002, 277: 44791-44800). The rocaglate silvestrol **2** displays cytotoxic activity against human cancer cells comparable to the anticancer drug Taxol (B.Y. Hwang *et al.*, J. Org. Chem., 2004, 69: 3350-3358).

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[4] As proposed by Proksch (P. Proksch *et al.*, Curr. Org. Chem., 2001, 5: 923-938) and Bacher (M. Bacher *et al.*, Phytochemistry, 1999, 52: 253-263), and as shown on Figure 2, the rocaglamides may be biosynthetically derived from reaction of trimethoxy-substituted 3-hydroxyflavone (3-HF) with cinnamide derivatives to afford the aglain core followed by skeletal rearrangement.

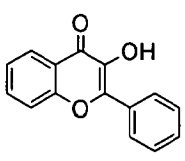
[5] Although the rocaglamides have been the subject of a number of synthetic investigations (see, for example, G.A. Kraus and J.O. Sy, J. Org. Chem., 1989, 54: 77-83; B. Trost *et al.*, J. Am. Chem. Soc., 1990, 112: 9022-9024), including a biomimetic approach involving a [2+2] photocycloaddition (H.C. Hailes *et al.*, Tetrahedron Lett., 1993, 34: 5313-5316), syntheses of the related aglain (V. Dumontet *et al.*, Tetrahedron, 1996, 52: 6931-6942), aglaforbesin (V. Dumontet *et al.*, Tetrahedron, 1996, 52: 6931-6942), or forbaglins have not been reported. Moreover, a unified synthetic approach to these molecules based on biosynthetic considerations still remains to be developed.

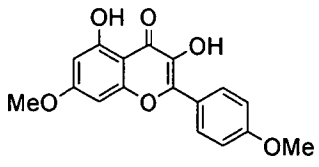
Summary of the Invention

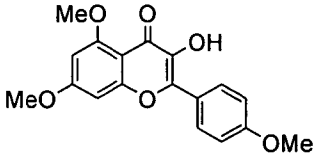
[6] The present invention provides new methods for the synthesis of natural products. In particular, the invention encompasses novel strategies for the biomimetic preparation of compounds in the rocaglamide/aglain/forbaglin family.

[7] More specifically, in one aspect, the present invention is related to the use of an oxidopyrylium species as a reactive intermediate in a chemical reaction, wherein the oxidopyrylium species is photochemically generated from a 3-hydroxyflavone derivative. The photochemical generation preferably proceeds *via* an excited state intramolecular proton transfer.

[8] In certain embodiments, the 3-hydroxyflavone derivative has one of the following chemical structures:







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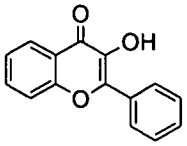
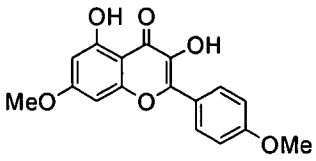
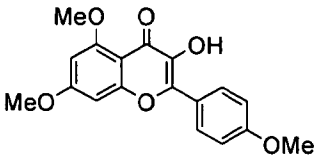
[9] In other embodiments, the oxidopyrylium species is used as an intermediate in a dipolar cycloaddition, for example, a 1,3-cycloaddition.

[10] In another aspect, the present invention is related to a method comprising steps of photochemically generating an oxidopyrylium species from a 3-hydroxyflavone derivative, preferably *via* excited state intramolecular proton transfer; and reacting the oxidopyrylium species thus obtained with a dipolarophile. In this inventive method, the 3-hydroxyflavone derivative preferably has one of the following chemical structures:



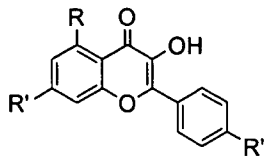




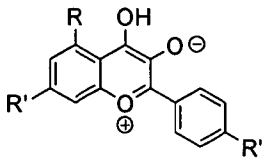
[11] In certain embodiments, the reaction between the oxidopyrylium species and dipolarophile (*e.g.*, a cinnamate derivative), comprises a dipolar cycloaddition, (*e.g.*, a 1,3-cycloaddition), and results in the formation of a cycloadduct. Preferably, the adduct comprises an aglain core structure.

[12] In other embodiments, the inventive method further comprises converting the adduct. For example, when the adduct formed comprises an aglain core structure, converting the adduct may result in the formation of a ring system selected from the group consisting of an aglain ring system, a rocaglamide ring system or a forbaglin ring system.

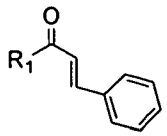
[13] In another aspect, the present invention provides a method for preparing a compound with an aglain core structure, wherein the method comprises steps of: producing an oxidopyrylium species (**II**) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**I**); and reacting the oxidopyrylium species obtained with a cinnamate derivative (**III**) to obtain the aglain core-containing compound (**IV**). Compounds (**I**), (**II**), (**III**), and (**IV**) have the following chemical structures:



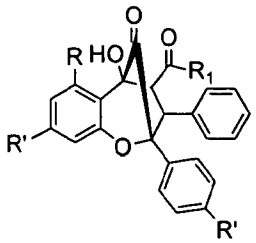
(I)



(II)



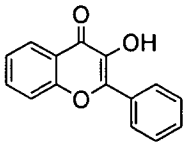
(III)

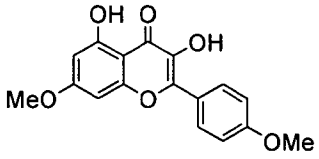


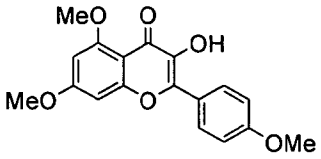
(IV)

wherein R and R' are identical or different and selected from the group consisting of hydrogen, hydroxy, methoxy, alkoxy, alkyl, aryl, and amino; and wherein R_1 is selected from the group consisting of alkyl, aryl, alkoxy, amino, and aminal.

[14] Preferably, compound (**I**) has one of the following chemical structures:







[15] In certain embodiments, the method further comprises converting the compound with an aglain core structure. For example, the aglain core-containing compound may be converted into a compound with a ring system selected from the group consisting of an aglain ring system, a rocaglamide ring system or a forbaglin ring system. Conversion into a compound with an aglain ring system may involve a reduction. Conversion into a compound with a rocaglamide ring system may comprise an α-ketol (acyloin) rearrangement (preferably under basic conditions), and optionally a hydroxyl-directed reduction. Conversion into a compound with a forbaglin ring system may comprise an oxidative cleavage.

[16] In another aspect, the present invention is related to a method for preparing an aglain derivative, which comprises steps of: producing an oxidopyrylium species (**II**) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**I**); reacting the oxidopyrylium species obtained with a cinnamate derivative (**III**) to obtain the aglain core-containing compound (**IV**); and converting the compound with an aglain core structure into an aglain derivative (**V**). Compounds (**I**), (**II**), (**III**), and (**IV**) are as described above and compound (**V**) has the following chemical structure:

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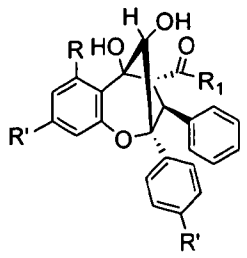
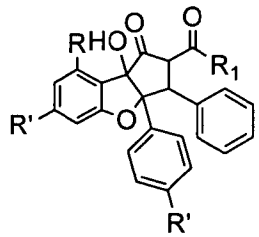


(V)

wherein R and R' are identical or different and selected from the group consisting of hydrogen, hydroxy, methoxy, alkoxy, alkyl, aryl, and amino; and wherein R_1 is selected from the group consisting of alkyl, aryl, alkoxy, amino, and aminal. Preferably, R and R' are methoxy groups.

[17] In certain preferred embodiments, converting the compound with an aglain core structure into an aglain derivative (**V**) involves for example, a reduction carried out in the presence of $NaBH_4$, $Me_4NBH(OAc)_3$ or another suitable reducing agent. Alternatively, addition of nucleophiles, *e.g.*, Grignard or alkylithium reagents, may be performed.

[18] In another aspect, the present invention is related to a method for preparing a rocaglamide derivative, which comprises steps of: producing an oxidopyrylium species (**II**) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**I**); reacting the oxidopyrylium species obtained with a cinnamate derivative (**III**) to obtain the aglain core-containing compound (**IV**); and converting the compound with an aglain core structure into a rocaglamide derivative (**VI**). Compounds (**I**), (**II**), (**III**), and (**IV**) are as described above and compound (**VI**) has the following chemical structure:



(VI)

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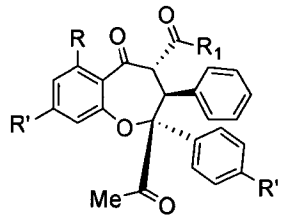
wherein R and R' are identical or different and selected from the group consisting of hydrogen, hydroxy, methoxy, alkoxy, alkyl, aryl, and amino and; and wherein R_1 is selected from the group consisting of alkyl, aryl, alkoxy, amino, and aminal.. Preferably, R and R' are methoxy groups.

[19] In certain preferred embodiments, converting the compound with an aglain core structure into a rocaglamide derivative (**VI**) comprises an α-ketol (acyloin) rearrangement and optionally a hydroxyl-directed reduction. Preferably, the α-ketol rearrangement is carried out under basic conditions.

[20] In another aspect, the present invention is related to a method for preparing a forbaglin derivative, which comprises steps of: producing an oxidopyrylium species (**II**) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**I**); reacting the oxidopyrylium species obtained with a cinnamate derivative (**III**) to obtain the aglain core-containing compound (**IV**); and converting the compound with an aglain core structure into a forbaglin derivative (**VII**). Compounds (I), (II), (III), and (IV) are as described above and compound (**VII**) has the following chemical structure:



(VII)

wherein R and R' are identical or different and selected from the group consisting of hydrogen, hydroxy, methoxy, alkoxy, alkyl, aryl, and amino; and wherein R_1 is selected from the group consisting of alkyl, aryl, alkoxy, amino, and aminal. Preferably, R and R' are methoxy groups.

[21] In certain preferred embodiments, converting the compound with an aglain core structure into a forbaglin derivative (**VII**) comprises an oxidative cleavage, for example, an oxidation carried out in the presence of $Pb(OAc)_4$.

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[22] In still another aspect, the present invention is related to the use of an oxidopyrylium species as an intermediate in a chemical reaction, wherein the oxidopyrylium species is photochemically generated from a 5-hydroxy-2,3-dihydro-pyran-4-one derivative. Preferably, the photochemical generation comprises an excited state intramolecular proton transfer. The oxidopyrylium species thus formed may be used as a reactive intermediate in a dipolar cycloaddition, for example, a 1,3-cycloaddition.

[23] In yet another aspect, the present invention provides methods comprising steps of: photochemically generating an oxidopyrylium species from a 5-hydroxy-2,3-dihydro-pyran-4-one derivative; and reacting the oxidopyrylium species with a dipolarophile, to obtain an adduct. Preferably, the photochemical generation comprises an excited state intramolecular proton transfer. Optionally, the adduct formed may be further converted.

Brief Description of the Drawing

[24] **FIG. 1** shows the chemical structures of Rocaglamide and related natural compounds isolated from the plant genus *Aglaia*.

[25] **FIG. 2** shows a reaction scheme proposed by Proksch and coworkers (Curr. Org. Chem., 2001, 5: 923-938) for the biosynthetic preparation of the rocaglamides.

[26] **FIG. 3** shows the new unified biomimetic approach to the synthesis of Aglains-Forbaglins-Rocaglamides.

[27] **FIG. 4** is a scheme showing the ESIPT process and fluorescence emission taking place upon photoirradiation of the parent molecule, 3-hydroxyflavone.

[28] **FIG. 5** shows the reaction of photochemical [3+2] cycloaddition between 3-hydroxyflavone **13** and methyl cinnamate **14**.

[29] **FIG. 6** shows the ^{1}H-NMR (400 MHz, $CDCl_3$) (**A**) and ^{13}C-NMR (75 MHz, $CDCl_3$) (**B**) spectra recorded for compound **16**, which results from photochemical [3+2] cycloaddition between 3-hydroxyflavone **13** and methyl cinnamate **14**.

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[30] **FIG. 7** shows a ^{1}H-NMR spectrum (400 MHz, CD_3CN) of a mixture of 3-hydroxy-flavone **13** (1 equivalent) and methyl cinnamate **14** (5 equivalents) after 2 hours of irradiation. The chemical structure of methyl cinnamate **14** is presented in red and the chemical structure of compound **16**, the main product of the reaction, is presented in blue.

[31] **FIG. 8** shows parts (3 to 5 ppm) of expanded ^{1}H-NMR spectra (400 MHz, CD_3CN) recorded for compound **16** (**FIG. 8(A)**); and for a mixture of 3-hydroxyflavone **13** and methyl cinnamate **14** after 2 hours of irradiation (**FIG. 8(B)**).

[32] **FIG. 9** shows the chemical conversion of an aglain core structure to forbaglin and rocaglamide ring systems.

[33] **FIG. 10** shows the ^{1}H-NMR (400 MHz, $CDCl_3$) (**A**) and ^{13}C-NMR (75 MHz, $CDCl_3$) (**B**) spectra recorded for compound **23**.

[34] **FIG. 11** is a scheme presenting the synthesis of (±) methyl rocaglate from trimethoxy-substituted 3-hydroxyflavone.

[35] **FIG. 12** shows the reaction sequence used to synthesize trimethoxy-substituted 3-hydroxyflavone **24**.

[36] **FIG. 13** shows the chemical structures of compound **27**, keto isomer **27'** and enol isomer **27"**.

[37] **FIG. 14** shows the ^{1}H-NMR (400 MHz, $CDCl_3$) (**A**) and ^{13}C-NMR (75 MHz, $CDCl_3$) (**B**) spectra recorded for compound **28**.

[38] **FIG. 15** shows the ^{1}H-NMR (400 MHz, $CDCl_3$) (**A**) and ^{13}C-NMR (75 MHz, $CDCl_3$) (**B**) spectra recorded for compound **29**.

[39] **FIG. 16** shows the HMQC spectrum of synthetic *exo* methyl rocaglate **29** (500 MHz, $CHCl_3$, 25°C).

[40] **FIG. 17** shows the HMBC spectrum of synthetic *exo* methyl rocaglate **29** (500 MHz, $CHCl_3$, 25°C).

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[41] **FIG. 18** shows the HMBC spectrum of synthetic *exo* methyl rocaglate **29** (500 MHz, $CHCl_3$, 25°C).

[42] **FIG. 19** shows the chemical structures of compounds **30** and **31**, obtained from chemical modifications of compounds **16** and **15**, respectively.

[43] **FIG. 20** shows the X-ray Crystal Structure of Compound **30**.

[44] **FIG. 21** shows the X-ray Crystal Structure of Compound **31**.

Detailed Description of Certain Preferred Embodiments

[45] The present invention is directed to a new, unified biomimetic approach to the synthesis of rocaglamides and the related aglains and forbaglins. This new approach is outlined in Figure 3. In particular, the new synthetic method involves photochemical generation of an oxidopyrylium species (compound **7**, in Fig. 3) *via* excited state intramolecular proton transfer (ESIPT) of a 3-hydroxyflavone derivative **6** followed by dipolar cycloaddition of the oxidopyrylium to a cinnamate derivative. Coupling of the photochemical reaction to the cycloaddition results in the formation of the adduct **8**, which contains an aglain core structure. Conversion of **8** by oxidative cleavage yields forbaglin **9**, while reduction of **8** produces aglain **10**. Core structure **8** may alternatively be converted to hydrorocaglate **11** by α-ketol (acyloin) rearrangement; and hydroxyl-directed reduction of **11** affords rocaglate **12**.

[46] The novel biomimetic approach to the synthesis of rocaglamides, aglains and forbaglins has been described, by the Applicants, in a recent scientific article (B. Gerard *et al.*, J. Am. Chem. Soc., 2004, in press), which is incorporated herein by reference in its entirety.

I. Excited State Intramolecular Proton Transfer (ESIPT)

[47] Literature reports have documented excited state intramolecular proton transfer (ESIPT) (see, for example, P.-T. Chou, J. Chin. Chem. Soc., 2001, 48: 651-682; A.D. Roschal *et al.*, J. Phys. Chem. A, 1998, 102: 5907-5914; A. Bader *et al.*, J. Phys. Chem. A, 2002, 106:

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2844-2849 and references therein; A. Samanta *et al.*, J. Phys. Chem. A, 2003; 107: 6334-6339; A.P. Demchenko, J. Phys. Chem. A, 2003, 107: 4211-4216; R. Rastogi *et al.*, Spectrochem. Acta, Part A, 2001, 57: 299-308) of 3-hydroxyflavone derivatives leading to the formation of the oxidopyrylium species (J. Hendrickson and J.S. Farina, J. Org.Chem., 1980, 45: 3359-3361; P.G. Sammes *et al.*, J. Chem. Soc. Perkin Trans. I, 1983, 1261-1265; P.A. Wender *et al.*, J. Am. Chem. Soc., 1997, 119: 12976-12977; J.E. Baldwin *et al.*, Tetrahedron Lett., 2003; 44: 4543-4545).

[48] The overall ESIPT process (shown on Figure 4 in the case of the parent molecule, 3-HF) involves generation of a putative tautomeric form of 3-HF, where the proton of the hydroxyl group at position C3 migrates to the ketone group at position C4 to give an oxidopyrylium species (tautomeric form **T**).

[49] Although ESIPT processes of 3-HF derivatives have been reported in the literature to produce excited state species such as the oxidopyrylium, there are no reports of chemical reactions with these potential intermediates.

[50] In this respect, the present invention is related to the use of an oxidopyrylium species as a reactive intermediate in a chemical reaction, wherein the oxidopyrylium species is photochemically generated from a 3-hydroxyflavone derivative *via* excited state intramolecular proton transfer. In preferred embodiments, the oxidopyrylium species is used as a reactive intermediate in a dipolar cycloaddition, such as a 1,3-cycloaddition.

II. Cycladdition Reactivity of Photochemically Generated Oxidopyrylium Species

[51] Initial efforts toward understanding the cycloaddition reactivity of the oxidopyrylium species **T** were focused on model studies using 3-hydroxyflavone, the parent compound and simplest molecule of the 3-hydroxyflavone family.

Oxidopyrylium Species Generated from 3-Hydroxyflavone

[52] Photoirradiation of 3-hydroxyflavone **13** in presence of the dipolarophile methyl cinnamate **14** was carried out in acetonitrile using a 450 W pressure mercury lamp (uranium

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filter, $\lambda > 350$ nm). After irradiation at room temperature for 2 hours, compound **13** was consumed and a mixture of products was obtained, resulting, presumably, from [3+2] cycloaddition (see Figure 5 and Example 1).

[53] Based on spectroscopic data and X-ray analysis of a crystalline derivative (see Example 1), the major compound (56%) was confirmed to be the *endo* cycloadduct **16** in which the phenyl ring of the dipolarophile is *anti* to the oxido bridge (P.G. Sammes and L.J. Street, J. Phys. Chem., 1998, 102: 5907-5914). ^{1}H- NMR and ^{13}C-NMR spectra recorded for compound **16** are presented in Figure 6.

[54] Interestingly, an equilibrium between **16** and the benzo[*b*]cyclobutapyran-8-one **17** is observed during silica gel purification resulting from an acid-mediated ketol shift (X. Creary *et al.*, J. Org. Chem., 1985, 50: 1932-1938). The equilibrium between the two core structures was found to be controlled by temperature: heating a mixture of compounds **16** and **17** (ethyl acetate, 65°C) was observed to lead to the formation of compound **16** exclusively. Monitoring of the photocycloaddition by ^{1}H-NMR (in CD_3CN) also confirmed formation of **16** as the major product (see Figure 7 and Figures 8(A) and 8(B)).

[55] Compound **15** (14%) was identified as a cyclopenta[*b*]tetrahydrobenzofuran by further conversion into a crystalline derivative. In contrast to **16**, compound **15** is derived from *exo* [3+2] cycloaddition to an aglaforbesin type ring system (see compound **4** in Figure 1) followed by acycloin rearrangement during the photoirradiation process (further experiments to support the ESIPT mechanism were conducted using 3-methoxyflavone). Irradiation (350 nm, acetonitrile, 5 equivalents of **18**, at room temperature) did not give a [3+2] cycloadduct but instead provided a product resulting from oxidative photocycloaddition (T. Matsuura and T. Takemo, Tetrahedron, 1973, 3337-3340).

***Conversion of Cycloadduct* 16**

[56] Cycloadduct **16**, which contains an aglain core structure, was then evaluated for its ability to be converted to compounds containing rocaglamide and forbaglin ring systems (as shown on Figure 9).

[57] Oxidative cleavage of the aglain core to the forbaglin ring system may be conducted using $Pb(OAc)_4$ (E. Baer, J. Am. Chem. Soc., 1940, 62: 1597-1606). Treatment of cycloadduct **16** with $Pb(OAc)_4$ in benzene/methanol at room temperature afforded benzo[*b*]oxepines **18:19** as a 2:1 mixture of keto-enol tautomers (85%) (see Example 2).

[58] The aglain core structure of compound **16** may alternatively be converted to dehydrorocaglate by α-ketol (acyloin) rearrangement (L.A. Paquette and J.E. Hofferberth, Org. React., 2003, 62: 477-567; for ketol shifts in biogenesis, see, for example, M. Rentzea and E. Hecker, Tetrahedron Lett., 1982, 23: 1785-1788; and D.H.G. Crout and D.L. Rathbone, J. Chem. Soc. Chem. Commun., 1987, 290-291)

[59] Attempted thermal acycloin rearrangement (J. Lui *et al.*, Tetrahedron, 1998, 54: 11637-11650) of compound **16** did not afford any observable ketol shift product. Acyloin rearrangements have alternatively been conducted using acidic or basic conditions or employing metal catalysis and have been used with success in a number of natural product syntheses (for K252a, see, for example, K. Tamaki *et al.*, Tetrahedron Lett., 2002, 43: 379-382; for Taxanes, see, for example, L. Paquette and J.E. Hofferberth, J. Org. Chem., 2003, 68: 2266-2275).

[60] Treatment of cycloadduct **16** with protic or Lewis acidic conditions (BF3, Et_2O, $ZnCl_2$) resulted in decomposition of the starting material. However, treatment of cycloadduct **16** under basic conditions (2.5 equivalents of NaOMe, methanol) (X. Creary *et al.*, J. Org. Chem., 1985, 50: 1932-1938), afforded a 1:1 mixture of keto-enol tautomers **20:21** (see Example 3). The success of basic conditions for α-ketol rearrangement may be explained by the fact that such basic conditions favor the formation of the enolate of **21**, which may drive the ketol shift equilibrium (E. Piers *et al.*, Synlett., 1999, 7: 1082-1084) towards the rocaglamide core.

[61] Further proof for this assumption was provided by treatment of cycloadduct **16** with NaH (2.1 equivalent, tetrahydrofuran, room temperature) and quenching of the reaction mixture with thionyl chloride, which led to the formation of the stable 1,3,2-dioxathiolane **22** (48 %) (M. Shipman *et al.*, Tetrahedron, 1999, 55: 108445-10850) (see Example 3).

[62] Hydroxyl-directed reduction (B. Trost *et al.*, J. Am. Chem. Soc., 1990, 112: 9022-9024) of **20:21** afforded rocagolate **23** (95 %) (see Example 4). The ^{1}H- NMR and ^{13}C-NMR spectra of compound **23** are presented on Figure 10.

Oxidopyrylium Species Generated from Methoxy-Substituted 3-Hydroxyflavone

[63] 3-Hydroxyflavone derivatives with methoxy substitutions were then evaluated for their suitability in the synthesis of rocaglamides and related compounds. The overall synthetic scheme is presented on Figure 11 in the case of the trimethoxy-substituted 3-hydroxyflavone.

[64] Trimethoxy-substituted 3-hydroxyflavone was synthesized following a procedure adapted from a reaction sequence reported by H. Tanaka and coworkers (Tetrahedron Lett., 2000, 41: 9735-9739) as shown in Figure 12.

[65] Photoirradiation (uranium filter) of kaempferol derivative **24** and methyl cinnamate **14** (Y.-J. Lee and T.-D. Wu, J. Chin. Chem. Soc., 2001, 48: 201-206) in methanol at 0°C afforded the aglain **25** as well as benzo[*b*]cyclobutapyran-8-one **26** (33 % and 17 %, respectively) after purification on SiO_2 (see Example 5).

Conversion of Compounds 25 and 26

[66] Basic conditions (NaOMe, methanol) were used to effect α-ketol rearrangement of compound **25** and compound **26** (see Example 6). In the case of compound **25**, the reaction led to the formation of a mixture of *endo* and *exo* cycloadducts **27**, in which the *endo* isomer was obtained as a mixture of keto-enol tautomers **27'/27"** (the chemical structures of compounds **27**, **27'** and **27"** are presented on Figure 12). In the case of compound **26**, the base-mediated reaction only gave the *endo* cycloadduct **27**.

[67] Hydroxyl-directed reduction of keto rocaglate **27**, which is described in Example 7, afforded (±)-methyl rocaglate **28** (51%) and the corresponding *exo* stereoisomer **29** (27 %) (B. Trost *et al.*, J. Am. Chem. Soc., 1990, 112: 9022-9024). The ^{1}H- NMR and ^{13}C-NMR spectra of compounds **28** and **29** are reported in Figure 14 and Figure 15, respectively.

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[68] Spectral data for synthetic compound **28** were in full agreement with those reported for natural methyl rocaglate (F. Ishibashi *et al.*, Phytochemistry, 1993, 32: 307-310) (see Example 7). Similarly, spectral data for synthetic **29** were in full agreement with those reported for natural methyl rocaglate (G.A. Kraus and J.O. Sy, J. Org. Chem., 1989, 54: 77-83).

III. Further Chemical Modifications of Aglain/Rocaglamide/Forbaglin Derivatives

[69] Initially formed aglain structures as well as the forbaglin and rocaglamide ring systems derived from them can be further chemically modified to obtain different derivatives in the aglain/rocaglamide/forbaglin family.

[70] Examples of such chemical modifications are described in Examples 8 and 9 in the case of compounds **16** and **15**, respectively. The chemical structures of the products of these chemical modifications (compound **30** and compound **31**, respectively) are shown on Figure 19.

Examples

[71] The following examples describe some of the preferred modes of making and practicing the present invention. However, it should be understood that these examples are for illustrative purposes only and are not meant to limit the scope of the invention. Furthermore, unless the description in an Example is presented in the past tense, the text, like the rest of the specification, is not intended to suggest that experiments were actually performed or data were actually obtained.

General Information

[72] Melting points were recorded on a Mel-Temp (Laboratory Devices). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. Methylene chloride, acetonitrile, methanol, and benzene were purified by passing through two packed columns of neutral alumina (Glass Contour, Irvine, CA). 3-Hydroxyflavone was purchased from Indofine Chemical Company, Inc. (Hillsborough, NJ).

Nuclear Magnetic Resonance

[73] ^{1}H-NMR spectra were recorded at 400 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. ^{13}C-NMR spectra were recorded at 75.0 MHz at ambient temperature with $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are reported in parts per million relative (ppm) to $CDCl_3$ (^{1}H, δ 7.24; ^{13}C, δ 77.0) or acetone-d_6 (^{1}H, δ 2.04; ^{13}C, δ 207.6, 30.0). Data for ^{1}H-NMR are reported as follows: chemical shift, integration, multiplicity (abbreviations are as follows: app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants. All ^{13}C-NMR spectra were recorded with complete proton decoupling.

Infrared Spectroscopy

[74] Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. Low and high-resolution mass spectra were obtained at the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer.

Chromatography

[75] HPLC analyses were carried out on an Agilent 1100 series HPLC (CHIRALCEL OD, Column No. OD00CE-AI015 and Agilent Zorbax SB-C18). Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates; and flash chromatography, using 200-400 mesh silica gel (Scientific Absorbents, Inc.).

Photochemical Irradiation

[76] Photochemistry experiments were performed using a Hanovia 450 W medium pressure mercury lamp housed in a water-cooled quartz immersion well or using an ethylene glycol cooling system (Neslab, RTE-140). Pyrex test tubes (16 x 100 mm) were mounted on a support approximately 0.5 cm from the immersion well lamp. An uranium filter was obtained from James Glass (Hanover, MA).

[77] All other reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

Example 1: Photochemical Irradiation of 3-Hydroxyflavone

Irradiation of 3-Hydroxyflavone in the Presence of Methyl Cinnamate

[78] To a (16 x 100 mm) test tube was added 3-hydroxyflavone **13** (400 mg, 1.7 mmol) and methyl cinnamate **14** (650 mg, 4 mmol) in 8 mL of anhydrous acetonitrile. After degassing with argon for 5 minutes, the mixture was irradiated (Hanovia UV lamp uranium filter, water used for cooling) at room temperature for 2 hours. The solution was concentrated in *vacuo* to afford a pink-yellow oil.

[79] Purification *via* flash chromatography (60:40 hexanes/EtOAc) yielded 92 mg (0.23 mmol, 15 %) of cyclopenta[*b*]tetrahydrobenzofuran **15** and 370 mg (0.94 mmol, 56 %) of a mixture of cyclopenta[*bc*]benzopyran **16** and benzo[*b*]cyclobutapyran-8-one **17** as colorless solid. Compound **17** was quantitatively converted to cyclopenta[*bc*]benzopyran **16** by thermolysis (EtOAc, 65°C, 4 hours).

[80] ***Cyclopenta[b]tetrahydrobenzofuran* 15.** White solid: mp 76-78°C; IR ν_{max} (film): 3449, 3064, 3033, 2955, 2920, 1740, 1697, 1682, 1596, 1476, 1254, 1223, 755 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46-6.97 (14 H, m), 4.48 (1 H, d, J = 13 Hz), 3.96 (1 H, d, J = 13 Hz), 3.59 (3 H, s), 3.01 (1 H, s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): 208.9, 168.8, 159.6, 136.9, 134.9, 132.1, 129.1, 129.0, 128.9, 128.3,134.9, 132.1, 129.1, 129.0, 128.9, 128.3, 127.9, 126.5, 125.8, 124.8, 122.5, 110.7, 94.0, 87.8, 59.3, 52.4, 52.3 ppm; HRMS (EI) m/z calculated for $C_{25}H_{20}O_5$, 400.1311; found, 401.1429 (M+H).

[81] ***Cyclopenta[bc]benzopyran* 16.** White solid: mp 78-81°C; IR ν_{max} (film): 3452, 3060, 3033, 2940, 1767, 1736, 1608, 1584, 1483, 1452, 1210, 905 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.82 (14 H, m), 4.631 (1 H, d, J = 9.2 Hz), 3.645 (1 H, d, J = 9.2 Hz), 3.606 (3 H, s), 3.57 (1 H, s) ppm; ^{13}C-NMR(75 MHz, $CDCl_3$) δ 208.4, 170.1, 150.9, 138.2, 133.4, 130.8, 129.8, 128.9, 128.7, 128.4, 128.0, 127.9, 127.5, 127.4, 127.3, 126.8, 126.6, 124.9, 122.1, 116.1, 85.1, 79.8, 57.0, 54.2, 52.8 ppm; HRMS (CI/NH_3) m/z calculated for $C_{25}H_{20}O_5$, 400.1311; found, 401.1357 (M+H).

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[82] ***Benzo[b]cyclobutapyran-8-one*** **17.** White solid: mp 68-70 °C; IR ν_{max} (film): 3448, 2922, 2851, 1743, 1597, 1558, 1475, 1248, 1055, 998, 965, 755 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (2 H, m), 7.25-6.95 (12 H, m), 4.25 (1 H, d, J = 8.8 Hz), 3.74 (1 H, d, J = 8.8 Hz), 3.55 (3 H, s), 3.27 (1 H, s) ppm; ^{13}C-NMR δ 190.33, 169.6, 151.5, 139.4, 135.4, 130.2, 129.9, 128.9, 128.7, 128.4, 128.1, 127.8, 127.5, 127.4, 126.8, 124.9, 124.6, 121.3, 116.5, 97.5, 88.6, 60.9, 54.3, 52.4 ppm; HRMS (CI/NH_3) m/z calculated for $C_{25}H_{20}O_5$, 400.1311; found, 401.1357 (M+H).

Example 2: Conversion of Cycloadduct 16 to a Forbaglin Ring System

[83] 50 mg of cyclopenta[*bc*]benzopyran **16** (0.125 mmol, 1 equiv) were dissolved in a mixture of methanol (30 %) and benzene (0.9 mL / 2.1 mL). $Pb(OAc)_4$ (55 mg, 0.125 mmol, 1 equivalent) was then added portionwise at room temperature and the reaction was stirred for 30 minutes at room temperature. After removal of the solvent *in vacuo*, the resulting residue was diluted with water (5 mL) and EtOAc (5 mL). After separation of the organic layer, the aqueous layer was further extracted twice with EtOAc (5 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (20 % EtOAc in hexane) afforded 46 mg (0.11 mmol, 85 %) of **18:19** as a colorless solid (2:1 mixture of keto/enol tautomers.

[84] ***Benzo[b]oxepines*** **18/19**. Colorless solid: mp 178-181°C; IR ν_{max} (film): 3060, 3033, 2959, 2924, 1759, 1747, 1684, 1602, 1444, 1434, 1308, 1244; 1102 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64-7.62 (2 H, d, J = 7.2 Hz), 7.44-7.28 (8 H, m), 7.18-7.16 (4 H, m), 5.12 (1 H, d, J = 10 Hz), 4.41 (1 H, d, J = 10 Hz), 3.66 (3 H, s), 3.16 (3 H, s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 193.2, 156.7, 154.2, 139.0, 134.8, 132.4, 129.2, 129.1, 128.9, 128.7, 128.3, 128.2, 127.8, 127.7, 127.6, 127.4, 126.9, 126.7, 122.3, 121.9, 121.8, 121.6, 64.9, 52.5, 52.2, 52.0, 51.8, 49.8, 46.7 ppm; HRMS (CI/NH_3) m/z calculated for $C_{26}H_{22}O_6$, 430.1416; found, 431.1516 (M+H).

Example 3: Conversion of Cycloadduct 16 to a Dehydrorocaglate Ring System

[85] To a solution of cyclopenta[*bc*]benzopyran **16** (50 mg, 0.125 mmol, 1 equivalent) in MeOH (3 mL) at room temperature was added a solution of NaOMe (17 mg, 0.31 mmol, 2.5 equivalents) in MeOH (1 mL) at room temperature. The resulting solution was stirred for 40 minutes at 65^{0}C. After quenching the reaction with saturated NH_4Cl at room temperature, 10 mL of EtOAc was added. The organic layer was separated and washed with water (2 x 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (20 % EtOAc in hexane) afforded 45 mg (0.11 mmol, 90 %) of the corresponding rocaglates **20/21** as a white solid.

[86] ***Cyclopenta[b]tetrahydrobenzofurans* 20/21**. White solid: mp 141-143°C IR ν_{max} (film): 3066, 3027, 2954, 2923, 2856, 1758, 1730, 1650, 1594, 1454, 1279, 1247, 1146, 975 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 1:1 mixture of keto/enol tautomers **20**:**21**) δ 7.52-6.88 (28 H, m), 5.28 (1 H, s), 4.13 (2 H, dd, J = 13.6 Hz), 3.63 (3 H, s), 3.57 (3 H, s), 2.66 (1 H, s), 2.10 (1 H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 167.1, 159.8, 132.6, 131.1, 128.8, 128.0, 127.8, 127.7, 127.6, 127.6, 127.3, 127.2, 126.9, 126.8, 126.6, 126.2, 125.3, 124.8, 122.6, 121.8, 119.5, 112.4, 110.6, 98.7, 57.4, 56.7, 55.8, 52.9, 51.7 ppm; HRMS (EI) m/z calculated for $C_{25}H_{20}O_5$, 400.1311; found, 401.1427 (M+H).

[87] To a solution of NaH (washed with 3 x 10 mL hexanes, 5 mg, 0.21 mmol, 2.1 equivalents) in THF (2 mL) was added a solution of cyclopenta[*bc*]benzopyran **16** (40 mg, 0.10 mmol, 1 equivalent) in THF (1 mL) at room temperature. The resulting yellow solution was stirred at room temperature for 30 minutes. After addition of thionyl chloride (15 μL, 0.21 mmol, 2.1 equivalents) at room temperature, the mixture was stirred for another hour and then quenched with saturated aqueous $NaHCO_3$. 10 mL of EtOAc were then added and the organic layer was washed with 2 × 3 mL of water and 3 mL brine. The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (5 % EtOAc in hexane) afforded 21 mg (0.048 mmol, 48 %) of the corresponding 1,3,2-dioxathiolane **22** as a yellow oil.

[88] ***1,3,2-Dioxathiolane* 22.** Yellow oil: IR ν_{max} (film): 3025, 2948, 2913, 1716, 1650, 1553, 1243, 1200, 746 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7. 46-7.07 (14 H, m), 3.85 (1 H, s),

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3.72 (3 H, s) ppm; ^{13}C-NMR δ 190.4, 165.4, 144.9, 143.1, 132.9, 132.6, 130.8, 130.3, 130.0, 129.6, 129.2, 128.8, 128.7, 128.5, 128.1, 125.6, 124.7, 122.6, 111.1, 52.6, 52.4 ppm; HRMS (EI) m/z calculated for $C_{25}H_{18}O_6S$, 446.0824; found, 447.0805 (M+H).

Example 4: Conversion of Dehydrorocaglate Ring System to Rocaglate Ring System

[89] To a solution of 197 mg (0.75 mmol, 6 equivalents) of $Me_4NBH(OAc)_3$ and 68 μL (1.25 mmol, 10 equivalents) of acetic acid in 3 mL of CH_3CN was added a solution of 50 mg (0.12 mmol, 1 equivalent) of keto rocaglate **20** in 1 mL of CH_3CN. The resulting yellow solution was stirred for 12 hours at room temperature before being quenched with 2 mL of saturated NH_4Cl solution. The solution was then treated with 1 mL of a 3 M aqueous solution of sodium/potassium tartrate and stirred at room temperature for 30 minutes. The aqueous solution was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (20 % EtOAc in hexane) afforded 30 mg (0.047 mmol, 95 %) of **23** as a white solid.

[90] ***Cyclopenta[b]tetrahydrobenzofuran* 23.** White solid: mp 176-178°C; IR ν_{max} (film): 3421, 3031, 2925, 1733, 1600, 1476, 1462, 1249, 1102, 976 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41-6.96 (14 H, m), 4.84 (1 H, d, *J* = 6 Hz), 4.50 (1 H, d, J = 13.6 Hz), 3.99 (1 H, dd, *J* = 6, 13.6 Hz), 3.66 (3 H, s,), 2.55 (1 H, s), 1.82 (1 H, s), ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.5, 159.1, 136.8, 134.5, 131.4, 127.9, 127.7, 127.6, 127.5, 127.4, 126.8, 126.5, 126.3, 121.6, 111.0, 100.8, 93.3, 79.2, 56.0, 52.2, 50.8 ppm; LRMS (ESI +) m/z calculated for $C_{25}H_{22}O_5$, 402.1467; found, 403.0 (M+H).

Example 5: Photochemical Irradiation of Methoxy-Substituted 3-Hydroxyflavone

Synthesis of Trimethoxy-Substituted 3-Hydroxyflavone

[91] Trimethoxy-substituted 3-hydroxyflavone **24** was synthesized following a procedure adapted from a reaction sequence reported by H. Tanaka and coworkers (Tetrahedron Lett., 2000, 41: 9735-9739). The reaction scheme is presented on Figure 12.

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Irradiation of Trimethoxy-Substituted 3-Hydroxyflavone in the Presence of Methyl Cinnamate

[92] To a (16 x 100 mm) test tube was added with kaempferol derivative **24** (200 mg, 0.61 mmol), methyl cinnamate **14** (990 mg, 6.1 mmol), and 20 mL of anhydrous methanol. After degassing with argon, the mixture was irradiated (Hanovia UV lamp, uranium filter) at 0°C for 12 hours under an argon atmosphere. The solution was concentrated in *vacuo* to give a yellow oil. Purification *via* flash chromatography (60:40 hexanes/EtOAc) afforded 100 mg (0.2 mmol, 33 %) of the corresponding trimethoxy cyclopenta[*bc*]benzopyran derivative **25** (mixture of *endo*/*exo* cycloadducts) as a white solid and 50 mg (0.1 mmol, 17 %) of benzo[*b*]cyclobutapyran-8-one derivative **26** as a yellow solid.

[93] ***Trimethoxy Cyclopenta[bc]benzopyran* 25.** White solid: mp 83-85°C. IR ν_{max} (film): 3475, 3013, 2943, 2832, 1786, 1737, 1611, 1590, 1510, 1450, 1255, 1146, 1094, 828 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54-7.52 (2 H, d, J = 8.8 Hz), 7.25-7.23 (2 H, d, J = 8.8 Hz), 7.17-7.49 (2 H, m), 7.10-7.04 (6 H, m), 6.85-6.82 (2 H, m), 6.64-6.60 (4 H, m), 6.19-6.18 (1 H, d, J = 2 Hz), 6.18-6.17 (1 H, d, J = 2 Hz), 6.11-6.10 (1 H, d, J = 2 Hz), 6.08-6.07 (1 H, d, J = 2 Hz), 4.49-4.47 (1 H, d, J = 9.2 Hz), 4.191-4.168 (1 H, d, J = 9.2 Hz), 3.94 (1 H, s), 3.84 (3 H, s), 3.83 (3 H, s), 3.77 (4 H, m), 3.75 (3 H, s), 3.71 (3 H, s), 3.66 (4 H, m), 3.62 (3 H, s), 3.55 (3H, s), 3.29 (1 H, s) ppm; ^{13}C-NMR (70 MHz, $CDCl_3$) δ 205.5, 170.7, 170.6, 161.9, 161.3, 158.8, 158.6, 158.4, 153.6, 152.8, 139.9, 138.1, 130.1, 129.8, 128.9, 128.7, 128.2, 127.8, 127.9, 127.0, 126.5, 125.6, 113.6, 112.7, 112.6, 107.7, 106.5, 97.9, 95.5, 94.4, 94.3, 93.6, 93.4, 92.7, 88.7, 83.6, 81.04, 80.7, 62.4, 57.6, 56.1, 55.9, 55.4, 55.3, 55.1, 54.5, 53.4, 52.2, 51.8 ppm; HRMS (CI/NH_3) m/z calculated for $C_{28}H_{26}O_8$, 490.1628; found, 491.1739 (M+H).

[94] ***Trimethoxy benzo[b]cyclobutapyran-8-one* 26.** Yellow solid: mp 79-81°C. IR ν_{max} (film): 3489, 3006, 2948, 2839, 1734, 1729, 1618, 1590, 1516, 1461, 1437, 1299, 1200, 1148, 1096, 909 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 (2 H, d, J = 8.8 Hz), 7.16 (2 H, m), 7.01 (3 H, m), 6.64 (2 H, d, J = 8.8 Hz), 6.19 (1 H, d, J = 2 Hz), 6.08 (1 H, d, J = 2 Hz), 4.27 (1 H, s), 4.17 (1 H, d, J = 9.6 Hz), 3.84 (4 H, m), 3.75 (3 H, s), 3.67 (3 H, s), 3.56 (3 H, s) ppm.

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Example 6: Conversion of Aglain 25 and Aglain 26 to a Keto Rocaglate Ring System

Conversion of Aglain 25

[95] To a solution of aglain **25** (60 mg, 0.12 mmol, 1 equivalent) in MeOH (4 mL) was added a solution of NaOMe (13.2 mg, 0.24 mmol, 2.5 equivalents) in MeOH (1 mL) at room temperature. The resulting solution was stirred for 40 minutes at 65°C. After quenching the reaction with saturated NH_4Cl, 10 mL of EtOAc was then added, and the organic layer was washed with water (2 x 5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 57 mg (0.12 mmol, 95 %) of crude ketol shift product **27/27'/27"** as a yellow oil which was used without further purification (3:1 mixture of *endo*:*exo* isomers **27'/ 27"** and **27,** see chemical structures of **27, 27', 27"** on Figure 13).

[96] ***Trimethoxy rocaglate* 27/27'/27".** Yellow oil: IR ν_{max} (film): 3501, 3006, 2947, 2926, 2839, 1762, 1734, 1615, 1513, 1450, 1440, 1255, 1213, 1146, 1033, 1076 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 1:1 mixture of keto/enol tautomers **27'** : **27"**) δ 7.34-7.32 (2 H, d, J = 6.8 Hz), 7.20-7.19 (2 H, m), 7.09-6.86 (15 H, m), 6.65 (2 H, d, J = 8.8 Hz), 6.51 (2 H., d, J = 6.8 Hz), 6.33 (1 H, d, J = 1.6 Hz), 6.17 (1 H, d, J = 1.6 Hz), 6.13 (1 H, d, J = 1.6 Hz), 6.12 (1 H, d, J = 1.6 Hz), 6.05 (1 H, d, J = 1.6 Hz), 6.00 (1 H, d, J = 1.6 Hz), 4.46 (1 H, s), 4.42 (1 H, d, J = 14.8 Hz), 4.36 (1 H, d, J = 14.8 Hz), 4.22 (1 H, d, J = 13.6 Hz), 4.04 (1 H, d, 13.6 Hz), 3.84 (3 H, s), 3.08-3.79 (9 H, m), 3.77 (9 H, m), 3.70 (6 H, m), 3.64 (6 H, m), 3.57 (3 H, s), 3.30 (1 H, s), 3.01 (1 H, s) ppm; HRMS (EI) m/z calculated for $C_{28}H_{26}O_8$, 490.1628; found, 490.9634 (M+H).

Conversion of Aglain 26

[97] Benzo[*b*]cyclobutapyran-8-one **26** was subjected to the aforementioned conditions using 20 mg (0.041 mmol, 1 equivalent) of **26** in MeOH (2 mL) and NaOMe (5 mg, 0.09 mmol, 2.5 equivalents) in MeOH (1 mL). 18 mg of crude ketol shift product **27** (0.036, 90 %) was isolated and used without further purification (only the *endo* isomer was isolated).

Example 7: Hydroxyl-Directed Reduction of Keto Rocaglate 27

Hydroxyl-Directed Reduction of Trimethoxy Keto Rocaglate 27

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[98] To a solution of 184 mg (0.70 mmol, 6 equivalents) of $Me_4NBH(OAc)_3$ and 63 μL (1.16 mmol, 10 equivalents) of acetic acid in 3 mL of CH_3CN was added a solution of 57 mg (0.12 mmol, 1 equivalent) of **27** in 1 mL of CH_3CN. The resulting yellow solution was stirred for 12 hours at room temperature before being quenched with 2 mL of saturated NH_4Cl. The solution was then treated with 1 mL of a 3 M aqueous solution of sodium/potassium tartrate and stirred at room temperature for 30 minutes. The aqueous solution was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification on silica gel (40 % EtOAc in hexane) afforded 30 mg (0.030 mmol, 51 %) of the corresponding *endo* methyl rocaglate **28** and 18 mg (0.017 mmol, 27 %) of the corresponding *exo* methyl rocaglate **29**.

[99] ***Endo Methyl Rocaglate* 28.** White solid: mp 92-93°C; R ν_{max} (film): 3013, 2954, 2926, 2853, 1734, 1615, 1517, 1457, 1433, 1262, 1195, 1150, 1031, 832 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.09 (2 H, d, J = 9.2 Hz), 7.05-7.03 (3 H, m), 6.84 (2 H, m), 6.65 (2 H, d, *J* = 9.2 Hz), 6.27 (1 H, d, *J* = 2 Hz), 6.1 (1 H, d, *J* = 2 Hz), 5.01 (1 H, dd, *J* = 6.4, 1.2 Hz), 4.28 (1 H, d, *J* = 14.4 Hz), 3.80 (1 H, dd, *J* = 14.4, 6.4 Hz), 3.86 (3 H, s), 3.82 (3 H, s), 3.69 (3 H, s), 3.63 (3 H, s), 3.50 (1 H, s), 1.81 (1 H, br) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5, 164.1, 160.9, 158.8, 157.0, 137.0, 129.0, 128.4, 127.8, 127.7, 126.5, 112.7, 107.7, 101.9, 93.7, 92.7, 89.5, 79.6, 60.4, 55.8, 55.1, 55.0, 51.9, 50.6 ppm; δ HRMS (CI/NH_3) m/z calculated for $C_{28}H_{28}O_8$, 492.1784; found, 493.1891 (M+H).

[100] ***Exo Methyl Rocaglate* 29.** Foamy yellow: solid mp 84-85°C. IR ν_{max} (film): 3031, 3006, 2958, 2936, 2846, 1730, 1636, 1430, 1307, 1258, 1132, 103 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 (2 H, d, *J* = 8.8 Hz), 7.17-1.15 (3 H, m), 6.95-6.94 (2 H, m), 6.87 (2 H, d, *J* = 8.8 Hz), 6.12 (1 H, d, *J* = 1.6 Hz), 6.06 (1 H, d, *J* = 1.6 Hz), 4.76 (1 H, dd, *J* = 10.2, 1.6 Hz), 4.02 (1 H, d, *J* = 12.8 Hz), 3.82 (3 H, s), 3.78 (3 H, s), 3.77 (3 H, s), 3.60 (3 H, s), 3.23 (1 H, dd, *J* = 12.8, 10.2 Hz), 1.81 (1 H, s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.1, 164.1, 162.0, 159.4, 157.9, 135.0, 129.1, 128.4, 128.0, 127.3, 119.7, 113.6, 105.1, 99.5, 92.6, 91.4, 88.8, 83.9, 55.8, 55.8, 55.4, 54.8, 52.3, 50.9 ppm; HRMS (CI/NH_3) m/z calculated for $C_{28}H_{28}O_8$, 492.1784; found, 493.1891 (M+H).

[101] The crude ketol shift product **27** obtained from benzo[*b*]cyclobutapyran-8-one derivative **26** was subjected to the aforementioned conditions using 58 mg of $Me_4NBH(OAc)_3$ (0.22 mmol, 6 equivalents), 20 μL (0.37 mmol, 10 equivalents) in 3 mL of MeCN, and 18 mg (0.037 mmol, 1 equivalent) of compound **26**. 13 mg of *endo* methyl rocaglate **28** (0.021 mmol, 75 %) was obtained.

[102] Tables 1, 2, and 3 shown below summarize data comparison of natural (F. Ishibashi *et al.*, Phytochemistry, 1993, 32: 307-310) and synthetic *endo* methyl rocaglate **28**.

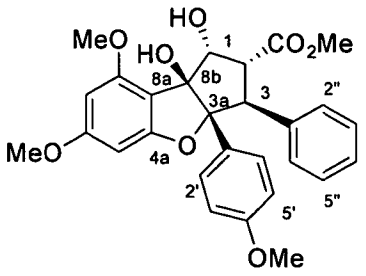

Table 1. ^{1}H-NMR Data (400 MHz, $CDCl_3$) for natural and synthetic *endo* methyl rocaglate **28**.

Position	^{1}H-NMR (400 Hz in $CDCl_3$)	
	Natural	Synthetic 28
1	5.02 (dd, 1.6, 6.8)	5.01 (dd, 1.2, 6.4)
2β	3.91 (dd, 6.8, 14.4)	3.91(dd, 6.4, 14.4)
3α	4.32 (d, 14.4)	4.27 (d, 14.4)
5	6.29 (d, 2.4)	6.26 (d, 2)
7	6.13 (d, 2.4)	6.10 (d, 2)
2', 6'	7.11 (d, 8.8)	7.10 (d, 9.2)
3', 5'	6.68 (d, 8.8)	6.65 (d, 9.2)
2", 6"	6.88 (m)	6.85 (m)
3", 4", 5"	7.07 (m)	7.04 (m)
OMe-6	3.88 (s)	3.86 (s)
OMe-8	3.84 (s)	3.81 (s)
OMe-4'	3.71 (s)	3.67 (s)
CO_2Me	3.65 (s)	3.62 (s)
OH	1.78, 3.60 (br, s)	1.88, 3.50 (br, s)

Table 2. ^{13}C-NMR Data (75 MHz, acetone-d_6) for natural and synthetic *endo* methyl rocaglate **28**.

Position	^{13}C NMR (75 Hz) in acetone d_6	
	Natural	Synthetic 28
1	80.6	80.3
2	51.5	51.1
3	55.8	55.5
3a	102.6	102.2
5	89.8	89.4
7	92.8	92.3
8a	112.8	112.4
8b	94.2	94.1
1'	128.9	128.4
2', 6'	129.9	129.6
3', 5'	112.8	112.4
1"	139.2	138.8
2", 6"	128.2	128.4
3", 5"	128.8	128.4
4"	126.8	126.4
4a, 6, 8, 4'	158.6, 159.3, 161.7, 164.6	158.3, 158.9, 161.4, 164.3
ArOMe	55.2, 55.9, 56.0	54.8, 55.3, 55.5
C=O	170.7	170.4
CO_2Me	51.5	51.1

Table 3. Miscellaneous data for natural and synthetic *endo* methyl rocaglate **28**

	Natural methyl rocaglate	**Synthetic methyl rocaglate 28**
Mp	88-91	92-93
HRMS (EI), *m/z* (rel. int.)	492.1797 $[M]^+$ 492 (3), 390 (6), 313 (46), 300 (100), 285 (59), 181 (66), 135 (78), 131 (50), 103 (55).	492.1814 $[M]^+$ 492 (2), 390 (5), 313 (40), 300 (100), 285 (23), 181 (21), 135 (16), 131 (24),
IR ν_{max} cm^{-1} (KBr)	3489, 1750, 1623, 1611, 1513, 1247, 1218, 1200, 1149, 1118	3486, 1734, 1615, 1517, 1251, 1212, 1195, 1150, 1115.

[103] Tables 4 and 5 shown below summarize data comparison of compound **29** and *exo* methyl rocaglate synthesized by Kraus and Sy (G.A. Kraus and J.O. Sy, J. Org. Chem., 1989, 54: 77-83).

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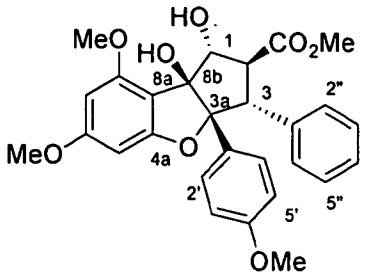

Table 4. ^{1}H-NMR Data (400 MHz, $CDCl_3$) for Kraus' *exo* methyl rocaglate and compound **29**.

Position	^{1}H NMR (400 Hz) in $CDCl_3$	
	Exo methyl rocaglate	29
1	4.77 (d, 11)	4.76 (dd, 1.6, 10.2)
2α	3.24 (dd, 11, 13)	3.23 (dd, 10.2, 12.8)
3β	4.03 (d, 13)	4.02(d, 12.8)
5	6.12 (d, 2)	6.12 (d, 1.6)
7	6.05 (d, 2)	6.06 (d, 1.6)
2', 6'	7.33 (d, 8)	7.34 (d, 8.8)
3', 5'	6.87 (d, 8)	6.87 (d, 8.8)
2", 6"	6.94 (m)	6.95 (m)
3", 4", 5"	7.16 (m)	7.16 (m)
Ar-OMe	3.81, 3.78, 3.76	3.82, 3.78, 3.77
CO_2Me	3.60	3.60

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Table 5. ^{13}C-NMR Data (75 MHz, $CDCl_3$)for Kraus'*exo* methyl rocaglate and compound **29**.

Position	^{13}C NMR (75 MHz) in $CDCl_3$	
	Exo methyl rocaglate	Compound 29
1	83.8	83.9
2	50.8	50.90
3	55.7	55.9
3a	91.2	91.4
5	88.7	88.7
7	92.5	92.6
8a	105.0	105.1
8b	99.3	99.5
1'	129.0	129.1
2', 6'	missing	119.6
3', 5'	113.5	113.6
1"	134.8	134.9
2", 6"	128.3	128.4
3", 5"	127.8	127.9
4"	127.1	127.3
4a, 6, 8, 4'	163.9, 161.9, 159.2, 156.8	164.1, 162.0, 159.4, 157.9
ArOMe	55.7, 55.3, 54.7	55.8, 55.4, 54.8
C=O	172.95	173.1
CO_2Me	52.1	52.3

Example 8: Reduction of Cyclopenta[*bc*]benzopyran 16

[104] To a solution of cyclopenta[*bc*]benzopyran **16** (100 mg, 0.25 mmol, 1 equivalent) in 10 mL of MeOH was added sodium borohydride (15 mg, 0.375 mmol, 1.5 equivalent) portionwise over 5 minutes at 0°C. The resulting solution was warmed to room temperature and stirred for 4 hours. The reaction was then quenched with saturated NH_4Cl, and diluted with EtOAc (10 mL) and water (10 mL). After separation of the organic layer, the aqueous layer was extracted twice with EtOAc (5 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

[105] The resulting diol (75 mg, 0.18 mmol, 1 equivalent) was directly subjected to acylation using 4-bromobenzoyl chloride (94 mg, 0.43 mmol, 1.2 equivalent) and DMAP

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(44 mg, 0.36 mmol, 2 equivalents) in 3 mL of CH_2Cl_2. The reaction was stirred at room temperature for 24 hours. The reaction mixture was diluted using CH_2Cl_2 (5 mL) and washed with water (2 x 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (30 % EtOAc in hexane) provided 95 mg (0.16 mmol, 85 %) of 4-bromobenzoate **30** as a colorless solid.

[106] ***4-Bromobenzoate* 30.** Colorless solid: mp 73-74 (benzene); IR ν_{max} (film): 3468, 3065, 3032, 2952, 2926, 2854, 1725, 1612, 1590, 1484, 1458, 1269, 911, 754; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46-7.43 (2 H. d, J = 10.2 Hz), 7.28-7.19 (6 H, m), 7.00-6.90 (10 H, m), 6.47 (1 H, s), 4.20-4.18 (1 H, s, 8.4 Hz), 3.80 (1 H, s), 3.63-3.61 (1 H, d, J = 8.4 Hz), 3.48 (3 H, s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.4, 166.2, 152.0, 139.2, 136.4, 131.7, 131.5, 129.9, 129.2, 128.8, 128.2, 127.9, 127.8, 127.7, 126.9, 126.5, 124.8, 123.6, 120.9, 115.7, 87.8, 77.8, 73.8, 60.5, 55.3, 52.4 ppm; HRMS (CI/NH_3) m/z calculated for $C_{32}H_{25}BrO_6$, 584.0835; found, 585.0931(M+H).

[107] The X-ray crystal structure of compound **30** is presented on Figure 20.

[108] Crystals of compound **30** suitable for X-ray analysis were obtained by slow evaporation from benzene. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 248425). Copies of the data can be obtained free of charge on application to the CCDC, (12 Union Road, Cambridge CB21EZ, UK; Fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[109] Crystal data and structure refinement for compound **30** are presented in Table 6.

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Table 6. Crystal data and structure refinement for compound **30**.

Identification code	Compound **30**	
Empirical formula	C50 H43 Br O6	
Formula weight	819.75	
Temperature	213(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.027(2) Å	α= 90°.
	b = 27.228(5) Å	β= 95.966(4)°
	c = 12.927(2) Å	γ = 90°
Volume	4210.2(13) $Å^3$	
Z	4	
Density (calculated)	1.293 Mg/m^3	
Absorption coefficient	1.026 mm^{-1}	
F(000)	1704	
Crystal size	0.10 x 0.08 x 0.08 mm^3	
Theta range for data collection	1.70 to 25.00°.	
Index ranges	-14<=h<=14, -32<=k<=26, -12<=l<=15	
Reflections collected	22422	
Independent reflections	7405 [R(int) = 0.1260]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7405 / 0 / 516	
Goodness-of-fit on F^2	0.998	
Final R indices [I>2sigma(I)]	R1 = 0.0655, wR2 = 0.1101	
R indices (all data)	R1 = 0.2038, wR2 = 0.1455	
Largest diff. peak and hole	0.504 and -0.513 $e.Å^{-3}$	

Example 9: Reactivity of Cyclopenta[*bc*]benzopyran 15

[110] To a solution of lithium aluminium hydride (26 mg, 0.89 mmol, 3 equivalents) in THF (5 mL) at 0°C was added a solution of cyclopenta[*b*]tetrahydrobenzofuran **15** (90 mg, 0.225 mmol, 1 equivalent) in 2 mL of THF. The resulting solution was warmed to room temperature and stirred for 3 hours. The reaction was then cooled at 0°C and quenched with 1 mL of water

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followed by 1 mL of 1 N aqueous NaOH. The resulting solution was filtered and the filtrate was evaporated *in vacuo* to afford the crude triol (63 mg, 0.17 mmol, 75 %).

[111] The crude triol was then directly subjected to acylation with 4-bromobenzoyl chloride (82 mg, 0.34 mmol, 2.2 equivalents) and DMAP (63 mg, 0.51 mmol, 3 equivalents) in 5 mL of CH_2Cl_2. The reaction was then stirred for 24 hours at room temperature. The mixture was diluted using CH_2Cl_2 (5 mL) and washed with water (2 x 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification on silica gel (30 % EtOAc in hexane) afforded 100 mg (0.14 mmol, 80 %) of *bis*-4-bromobenzoate **31** as a colorless solid,

[112] ***Bis-4-bromobenzoate*** **31.** Colorless solid: mp 256-257°C (petroleum ether / chloroform); IR ν_{max} (film): 3420, 3035, 2956, 2870, 1717, 1701, 1590, 1475, 1465, 1398, 1365, 1271, 1216, 1125 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70-7.68 (2 H, d, J = 8.4 Hz), 7.59-7.56 (2 H, d, J = 8.4 Hz), 7.51-7.48 (2 H, d, J = 8.4 Hz),7.40-7.18 (14 H, m), 6.98-6.59 (2 H, d, J = 8.4 Hz), 5.93 (1 H, d, J = 11.2 Hz), 4.53 (1 H, dd, J = 11.2, 8.4 Hz), 4.33 (1 H, dd, J = 11.2, 5.6 Hz), 3.53 (1 H, m), 3.19 (1 H, dd, J = 12.4, 11.6 Hz), 2.98 (3 H, s) 2.01 (1 H, s) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.2, 165.4, 159.6, 137.5, 137.0, 131.8, 131.3, 131.2, 131.0, 129.0, 128.7, 128.4, 128.2, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 126.7, 126.5, 121.5, 110.1, 97.5, 89.3, 86.8, 62.9, 50.4, 48.4, 29.6 ppm; δ HRMS (CI/NH_3) m/z calculated for $C_{38}H_{28}Br_2O_6$, 738.0253; found, 739.0217 (M+H).

[113] The X-ray crystal structure of compound **31** is presented on Figure 21. Crystals of compound **31** suitable for X-ray analysis were obtained by slow evaporation from benzene. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 248425).

[114] Crystal data and structure refinement for compound **31** are presented in Table 7.

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Table 7. Crystal data and structure refinement for compound **31**.

Identification code	Compound **31**	
Empirical formula	C38 H28 Br2 O6	
Formula weight	740.42	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 25.4111(10) Å	α= 90°.
	b = 16.5031(6) Å	β= 106.6770(10)°°
	c = 16.4599(6) Å	γ = 90°
Volume	6612.3(4) $Å^3$	
Z	8	
Density (calculated)	1.488 Mg/m^3	
Absorption coefficient	2.498 mm^{-1}	
F(000)	2992	
Crystal size	0.40 x 0.15 x 0.03 mm^3	
Theta range for data collection	0.84 to 20.81°	
Index ranges	-25<=h<=25, -13<=k<=16, -14<=l<=16	
Reflections collected	23839	
Independent reflections	6644 [R(int) = 0.0507]	
Completeness to theta = 25.00°	95.9 %	
Absorption correction	None	
Refinement method	Semiempirical by SADABS	
Data / restraints / parameters	6644 / 0 / 829	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2sigma(I)]	R1 = 0.0940, wR2 = 0.1169	
R indices (all data)	R1 = 0.2038, wR2 = 0.1455	
Largest diff. peak and hole	0.385 and -0.467 $e.Å^{-3}$	

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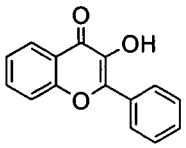
Claims

What is claimed is:

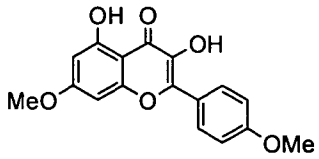
1. Use of an oxidopyrylium species as a reactive intermediate in a chemical reaction, wherein the oxidopyrylium species is photochemically generated from a 3-hydroxy-flavone derivative.

2. The use as in claim 1, wherein the photochemical generation comprises an excited state intramolecular proton transfer.

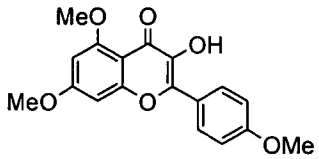
3. The use as in claim 1, wherein the 3-hydroxyflavone derivative has the following chemical structure:



4. The use as in claim 1, wherein the 3-hydroxyflavone derivative has the following chemical structure:



5. The use as in claim 1, wherein the 3-hydroxyflavone derivative has the following chemical structure:



6. The use as in claim 1, wherein the chemical reaction comprises a dipolar cycloaddition.

7. The use as in claim 6, wherein the dipolar cycloaddition is a 1,3- dipolar cycloaddition.

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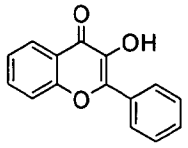
8. A method comprising steps of:

photochemically generating an oxidopyrylium species from a 3-hydroxyflavone derivative; and

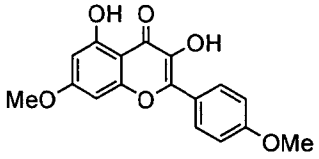
reacting the oxidopyrylium species obtained with a dipolarophile.

9. The method of claim 8, wherein the photochemical generation comprises an excited state intramolecular proton transfer.

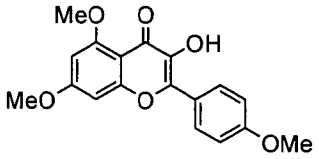
10. The method of claim 8, wherein the 3-hydroxyflavone derivative has the following chemical structure:



11. The method of claim 8, wherein the 3-hydroxyflavone derivative has the following chemical structure:



12. The method of claim 8, wherein the 3-hydroxyflavone derivative has the following chemical structure:



13. The method of claim 8, wherein the reaction between the oxidopyrylium species and the dipolarophile comprises a dipolar cycloaddition.

14. The method of claim 13, wherein the dipolar cycloaddition is a 1,3-cycloaddition.

15. The method of claim 8, wherein the dipolarophile is a cinnamate derivative.

16. The method of claim 8, wherein said method results in the formation of an adduct.

17. The method of claim 16 further comprising converting the adduct formed.

18. The method of claim 16, wherein the adduct comprises an aglain core structure.

19. The method of claim 18 further comprising converting the aglain core structure.

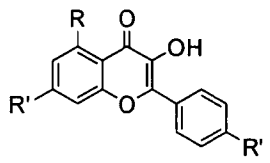
20. The method of claim 19, wherein converting the aglain core structure results in the formation of a ring system selected from the group consisting of an aglain ring system, a rocaglamide ring system, and a forbaglin ring system.

21. A method for preparing a compound with an aglain core structure, the method comprising steps of:

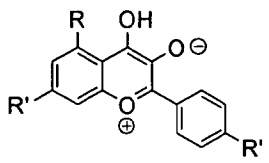
producing an oxidopyrylium species (**II**) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**I**); and

reacting the oxidopyrylium species with a cinnamate derivative (**III**) to obtain the aglain core-containing compound (**IV**),

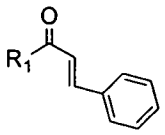
wherein compounds (**I**), (**II**), (**III**) and (**IV**) have the following chemical structures:



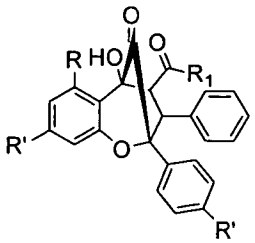
(**I**)



(**II**)



(**III**)



(**IV**)

wherein R and R' are identical or different and selected from the group consisting of hydrogen, hydroxy, methoxy, alkoxy, alkyl, aryl, and amino; and wherein R_1 is selected from the group consisting of alkyl, aryl, alkoxy, amino, and aminal.

22. The method of claim 21, wherein R' is hydroxy and R is hydrogen.

23. The method of claim 21, wherein R' is methoxy and R is hydroxy.

24. The method of claim 21, wherein R and R' are methoxy.

25. The method of claim 21 further comprising converting the compound with an aglain core structure.

26. The method of claim 25, wherein converting the compound with an aglain core structure results in the formation of a compound with a ring system selected from the group consisting of an aglain ring system, a rocaglamide ring system, and a forbaglin ring system.

27. The method of claim 21 further comprising converting the compound with an aglain core structure into a compound with an aglain ring system.

28. The method of claim 27, wherein converting the compound with an aglain core structure into a compound with an aglain ring system comprises a reduction.

29. The method of claim 21 further comprising converting the compound with an aglain core structure into a compound with a rocaglamide ring system.

30. The method of claim 29, wherein converting the compound with an aglain core structure into a compound with a rocaglamide ring system comprises an α-ketol (acyloin) rearrangement.

31. The method of claim 29, wherein converting the compound with an aglain core structure into a compound with a rocaglamide ring system comprises an α-ketol (acyloin) rearrangement and a hydroxyl-directed reduction.

32. The method of claim 30 or 31, wherein the α-ketol (acyloin) rearrangement comprises a base-mediated reaction.

33. The method of claim 21 further comprising converting the compound with an aglain core structure into a compound with a forbaglin ring system.

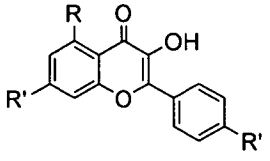
34. The method of claim 33, wherein converting the compound with an aglain core structure into a compound with a forbaglin ring system comprises an oxidative cleavage

35. A method for preparing an aglain derivative, the method comprising steps of:

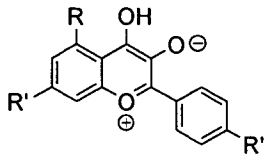
producing an oxidopyrylium species (**II**) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**I**);

reacting the oxidopyrylium species with a cinnamate derivative (**III**) to obtain a compound with an aglain core structure (**IV**); and

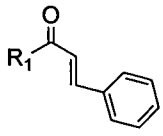
converting the compound with an aglain core structure into an aglain derivative (**V**), wherein compounds (**I**), (**II**), (**III**), (**IV**) and (**V**) have the following chemical structures:



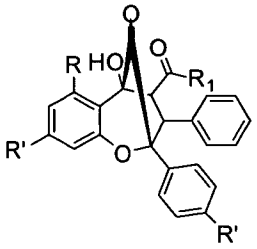
(**I**)



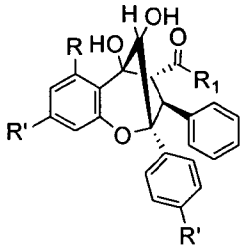
(**II**)



(**III**)



(**IV**)



(**V**)

wherein R and R' are identical or different and selected from the group consisting of hydrogen, hydroxy, methoxy, alkoxy, alkyl, aryl, and amino; and wherein R_1 is selected from the group consisting of alkyl, aryl, alkoxy, amino, and aminal.

36. The method of claim 35, wherein converting the compound with an aglain core structure into an aglain derivative (**V**) comprises a reduction.

37. The method of claim 36, wherein the reduction comprises using $NaBH_4$ or $Me_4BH(OAc)_3$.

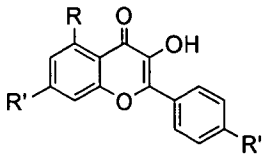
38. The method of claim 35, wherein R and R' are methoxy.

39. A method for preparing a rocaglamide derivative, comprising steps of:

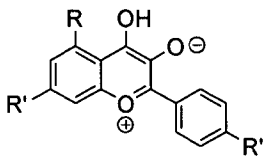
producing an oxidopyrylium species (**II**) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**I**);

reacting the oxidopyrylium species obtained with a cinnamate derivative (**III**) to obtain a compound with an aglain core structure (**IV**); and

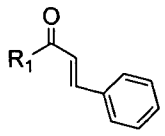
converting the compound with an aglain core structure into a rocaglamide derivative (**VI**), wherein compounds (**I**), (**II**), (**III**), (**IV**), and (**VI**) have the following chemical structures:



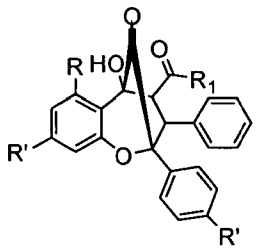
(**I**)



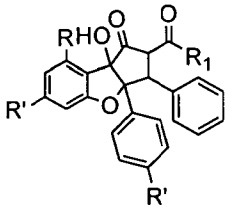
(**II**)



(**III**)



(**IV**)



(**VI**)

wherein R and R' are identical or different and selected from the group consisting of hydrogen, hydroxy, methoxy, alkoxy, alkyl, aryl, and amino; and wherein R_1 is selected from the group consisting of alkyl, aryl, alkoxy, amino and aminal.

40. The method of claim 39, wherein converting the compound with an aglain core structure into a rocaglamide derivative (**VI**) comprises an α-ketol (acyloin) rearrangement.

41. The method of claim 39, wherein converting the compound with an aglain core structure into a rocaglamide derivative (**VI**) comprises an α-ketol (acyloin) rearrangement and a hydroxyl-directed reduction.

42. The method of claim 40 or 41, wherein the an α-ketol (acyloin) rearrangement comprises a base-mediated reaction.

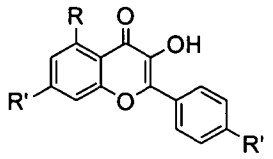
43. The method of claim 39, wherein R and R' are methoxy.

44. A method for preparing a forbaglin derivative, the method comprising steps of:

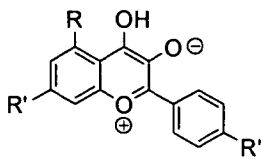
producing an oxidopyrylium species (**II**) by photoinduced excited state intramolecular proton transfer of a 3-hydroxyflavone derivative (**I**);

reacting the oxidopyrylium species obtained with a cinnamate derivative (**III**) to obtain a compound with an aglain core structure (**IV**); and

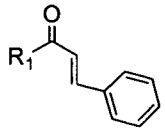
converting the compound with an aglain core into a forbaglin derivative (**VII**), wherein compounds (**I**), (**II**), (**III**), (**IV**) and (**VII**) have the following chemical structures:



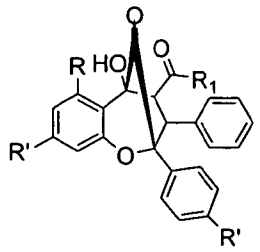
(**I**)



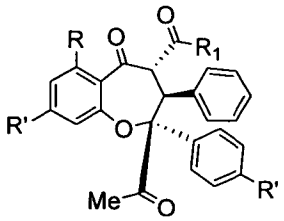
(**II**)



(**III**)



(**IV**)



(**VII**)

wherein R and R' are identical or different and selected from the group consisting of hydrogen, hydroxy, methoxy, alkoxy, alkyl, aryl, and amino; wherein R_1 is selected from the group consisting of alkyl, aryl, alkoxy, amino, and aminal.

45. The method of claim 44, wherein converting the compound with an aglain core structure into a forbaglin derivative (**VII**) comprises an oxidative cleavage.

46. The method of claim 45, wherein the oxidative cleavage comprise using $Pb(OAc)_4$.

47. Use of an oxidopyrylium species as a reactive intermediate in a chemical reaction, wherein the oxidopyrylium species is photochemically generated from a 5-hydroxy-2,3-dihydro-pyran-4-one derivative.

48. The use as in claim 47, wherein the photochemical generation comprises an excited state intramolecular proton transfer.

49. The use as in claim 47, wherein the chemical reaction comprises a dipolar cycloaddition.

50. The use as in claim 49, wherein the dipolar cycloaddition is a 1,3-dipolar cycloaddition.

51. A method comprising steps of:

photochemically generating an oxidopyrylium species from a 5-hydroxy-2,3-dihydro-pyran-4-one derivative; and

reacting the oxidopyrylium species obtained with a dipolarophile.

52. The method of claim 51, wherein the photochemical generation comprises an excited state intramolecular proton transfer.

53. The method of claim 51, wherein said method results in the formation of an adduct.

54. The method of claim 53 further comprising converting the adduct obtained.

Abstract

[115] The present invention provides new strategies for the synthesis of compounds of the rocaglamide family and related natural products. In particular, the new biomimetic synthetic approach involves the photochemical generation of an oxidopyrylium species from a 3-hydroxyflavone derivative followed by dipolar cycloaddition of the oxidopyrylium species to a cinnamate molecule. This reaction sequence leads to the formation of an adduct containing an aglain core. The invention also provides methods for the conversion of the aglain core structure to the aglain, rocaglamide and forbaglin ring systems.

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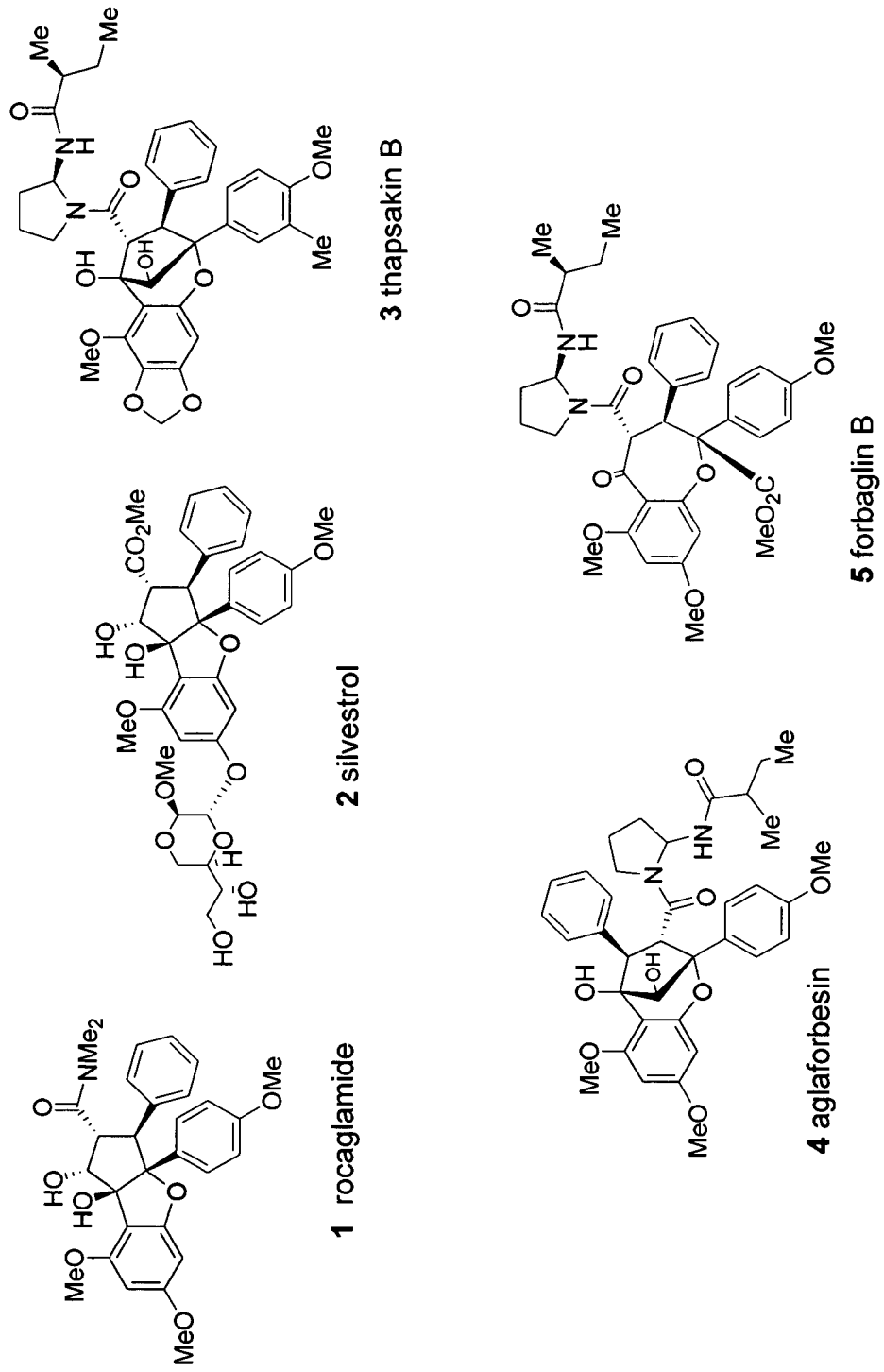

3 thapsakin B
2 silvestrol
5 forbaglin B
1 rocaglamide
4 aglaforbesin

Figure 1

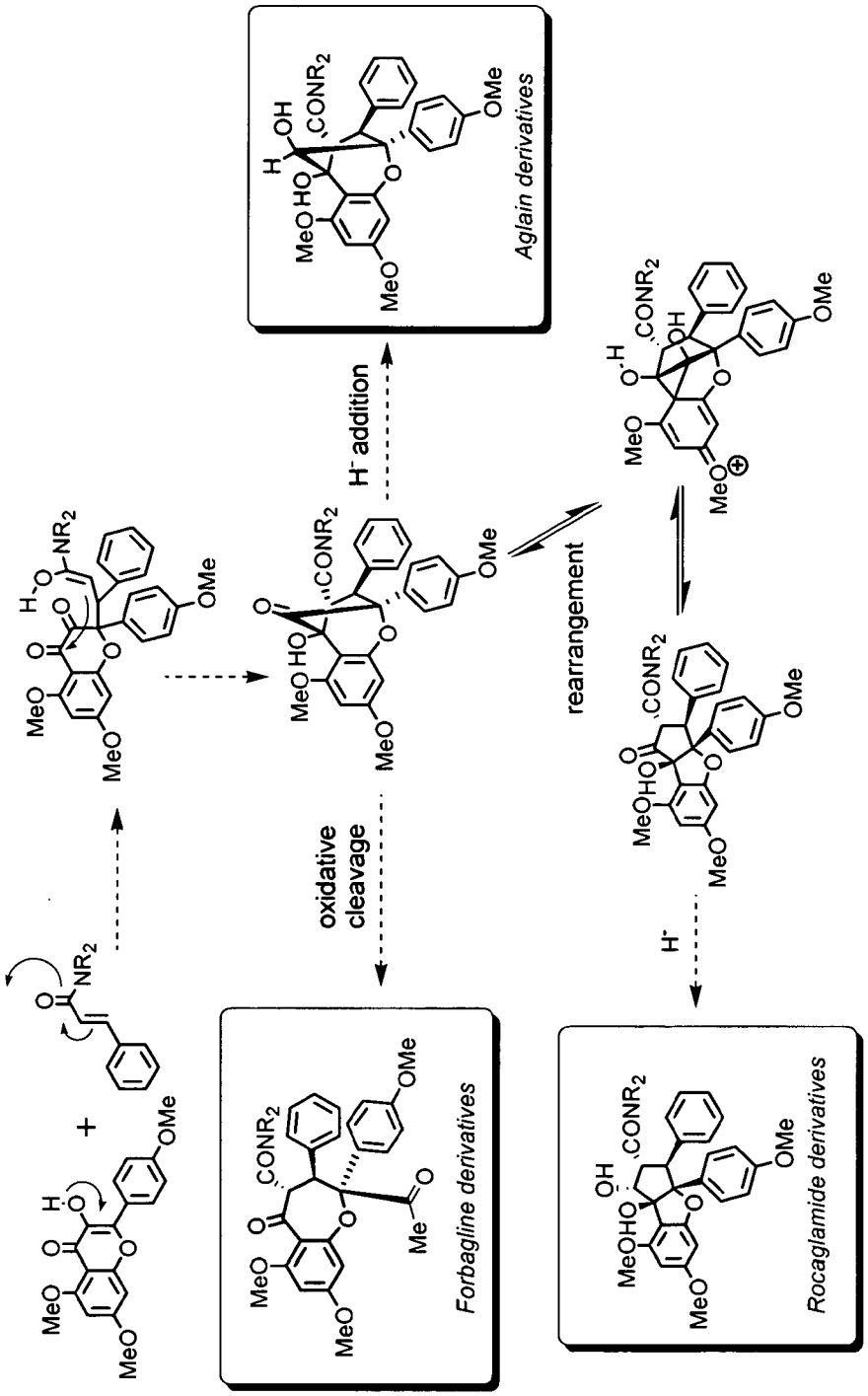

Aglain derivatives
H⁻ addition
rearrangement
oxidative cleavage
Forbagline derivatives
Rocaglamide derivatives
H⁻

Figure 2

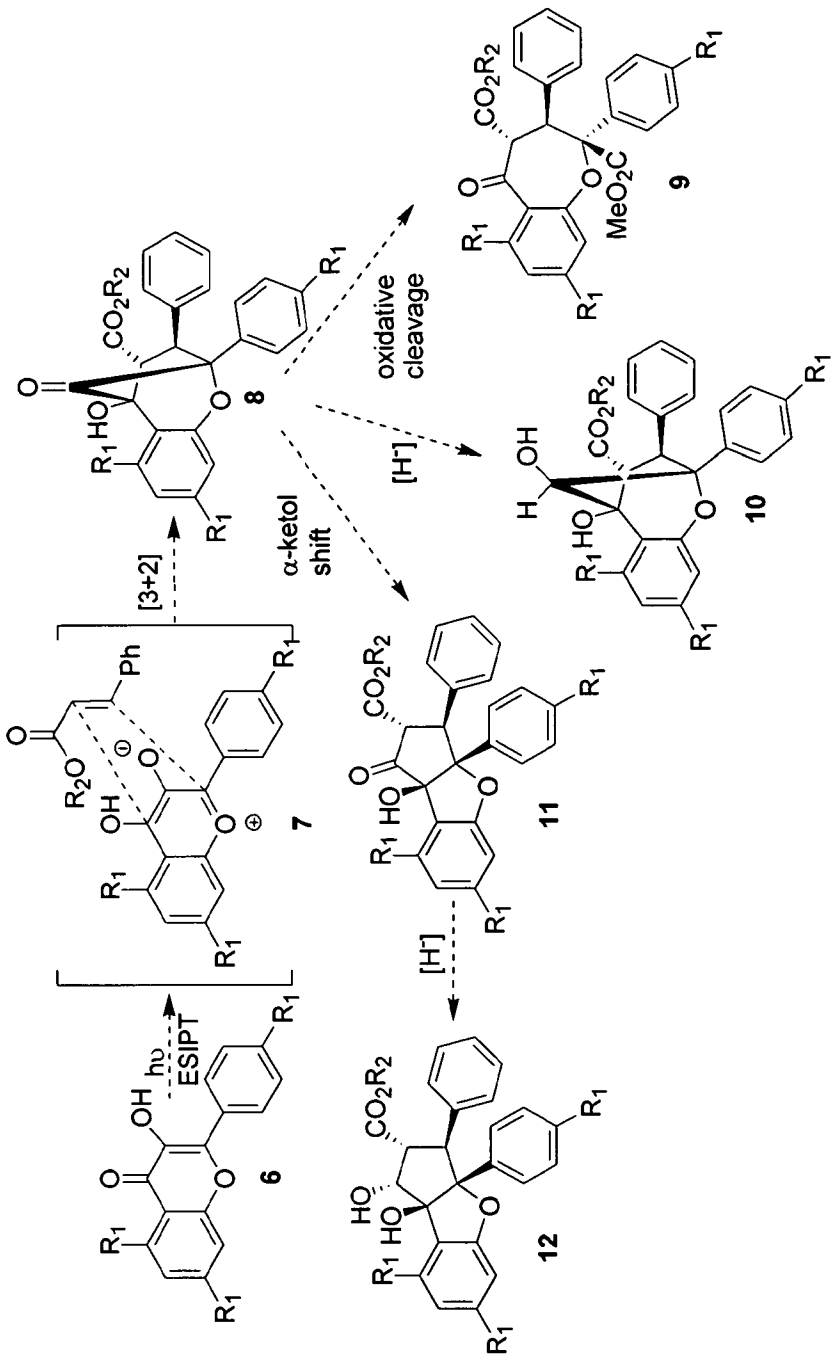


Figure 3

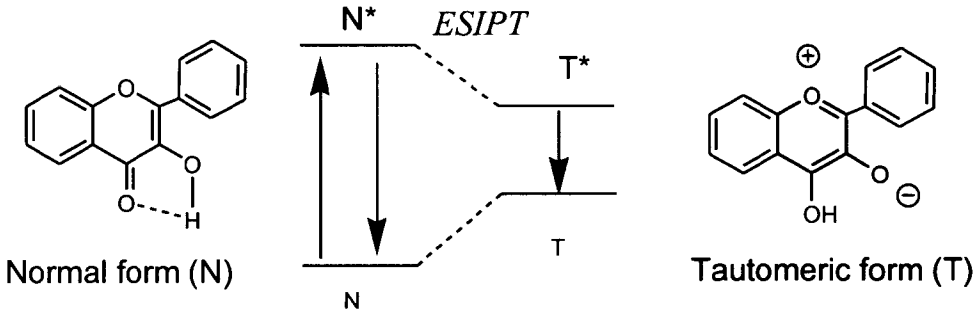


Figure 4

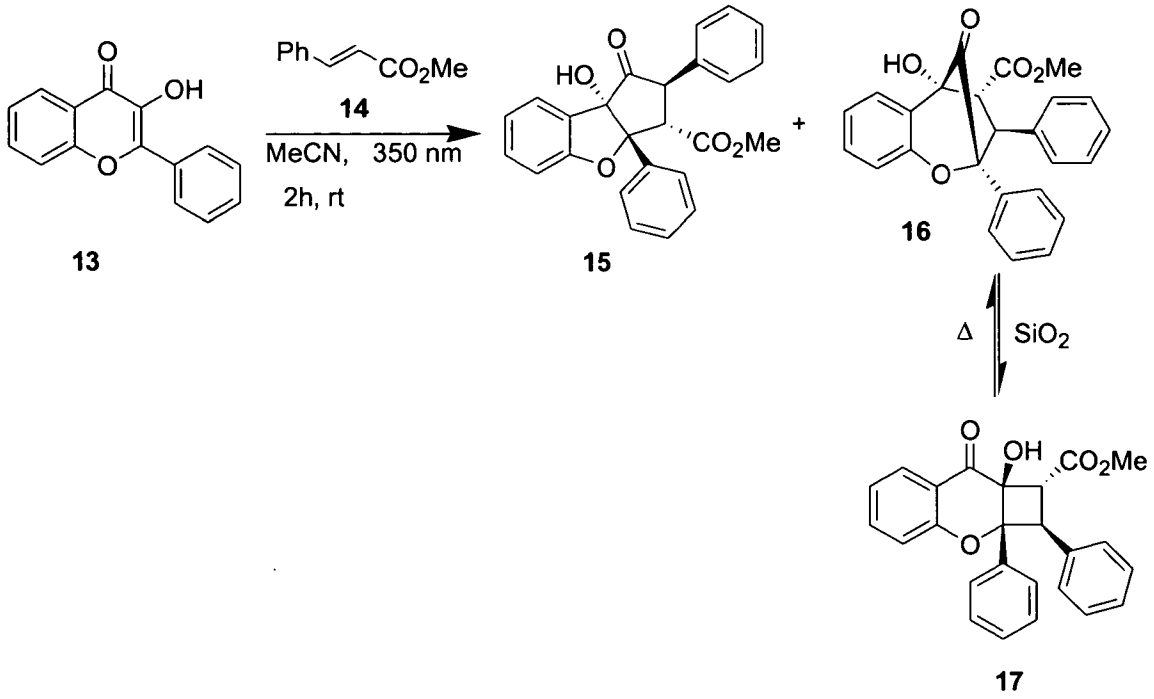

O
OH
O
13
Ph
CO2Me
14
MeCN, 350 nm
2h, rt
HO
O
CO2Me
O
15
+
HO
O
CO2Me
O
16
Δ
SiO2
O
OH
CO2Me
O
17

Figure 5

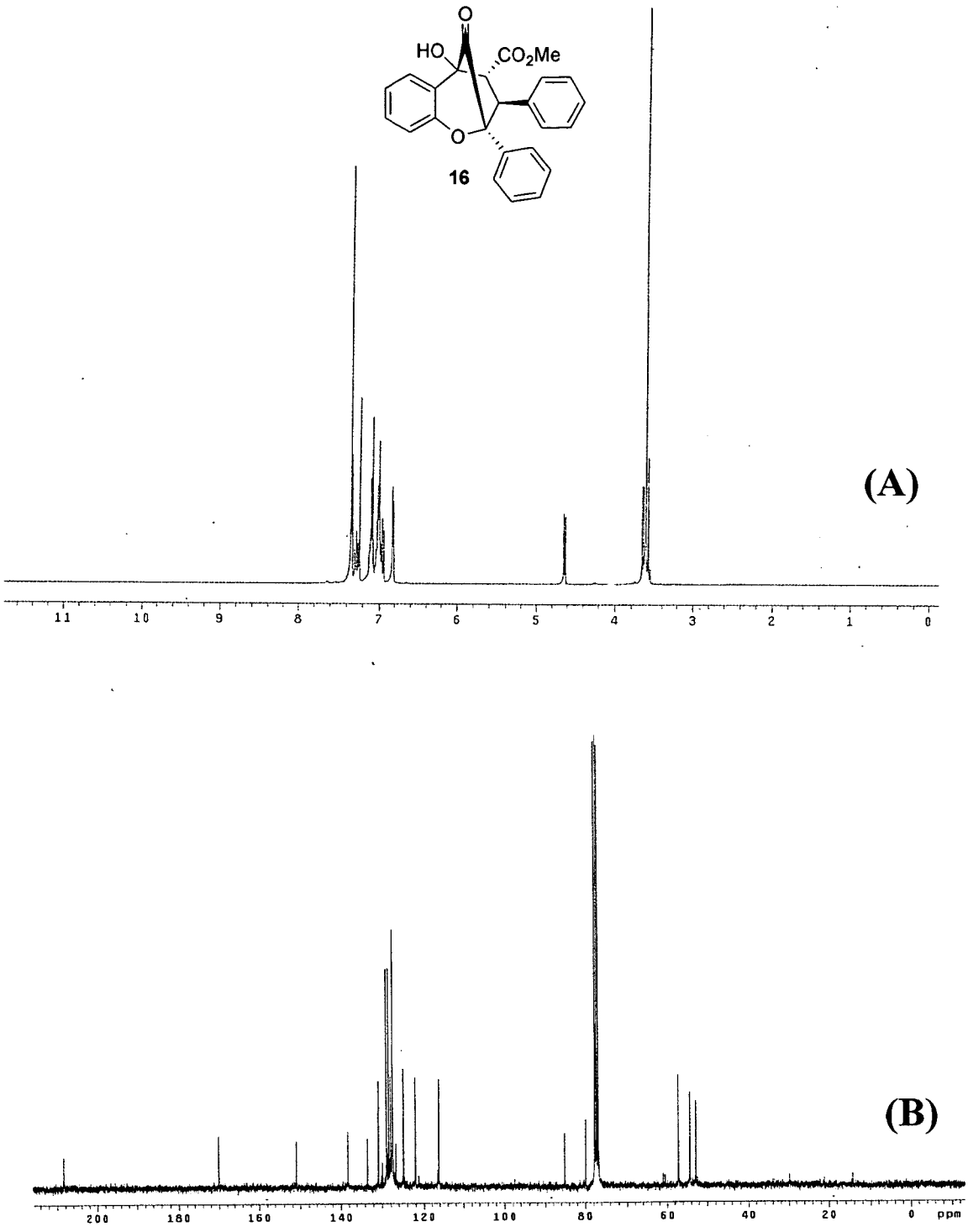

HO
CO2Me
O
O
16
(A)
11
10
9
8
7
6
5
4
3
2
1
0
(B)
200
180
160
140
120
100
80
60
40
20
0
ppm

Figure 6

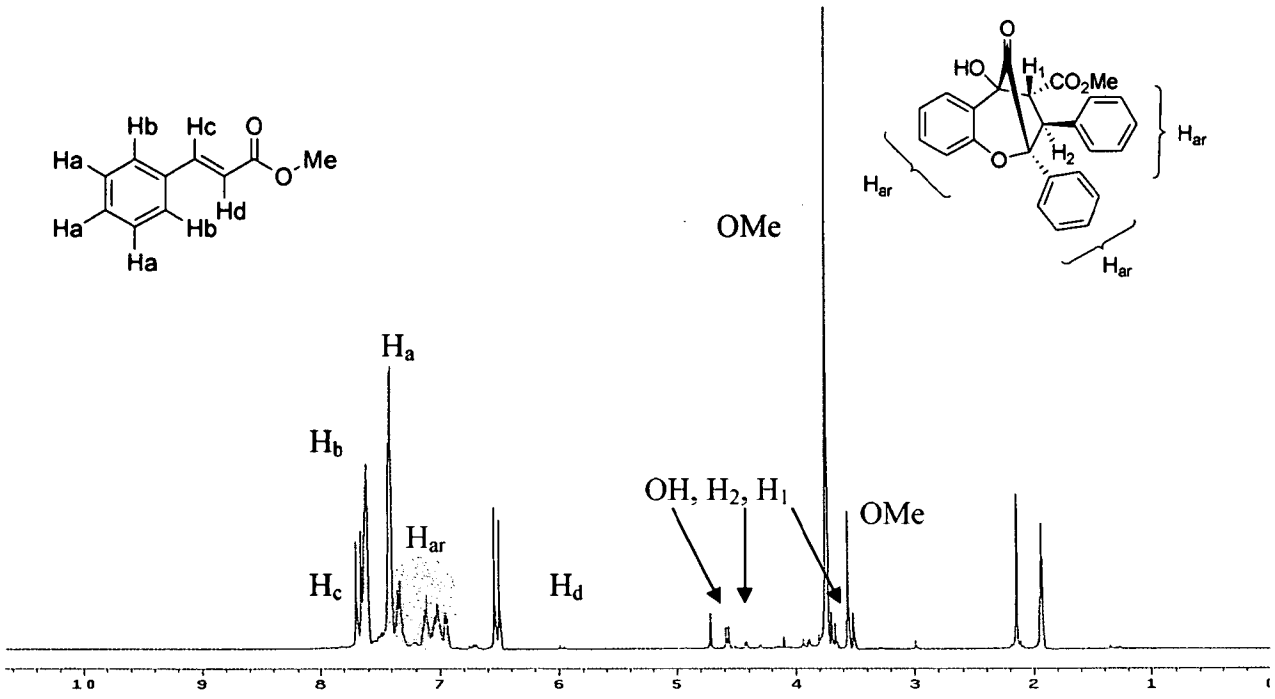
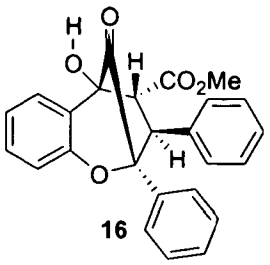

Hb
Hc
O
Ha
Me
O
Hd
Ha
Hb
Ha
HO
H1
CO2Me
Har
H2
O
Har
Har
OMe
Ha
Hb
Har
Hc
Hd
OH, H2, H1
OMe
10
9
8
7
6
5
4
3
2
1

Figure 7



16

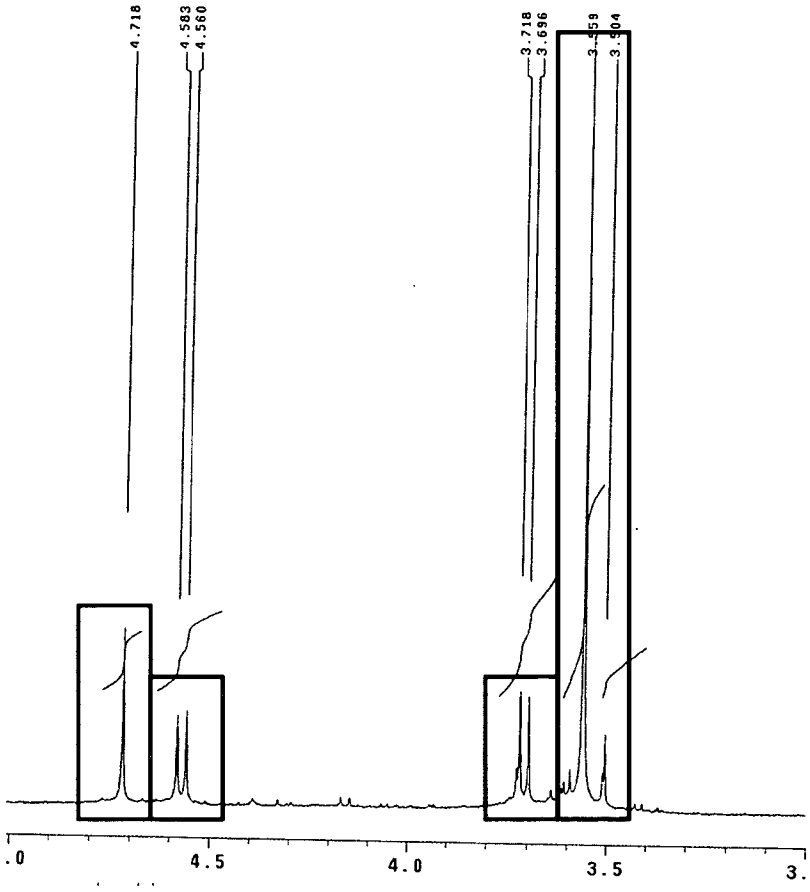
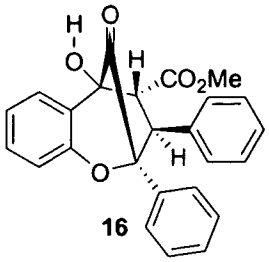


Figure 8(A)


H
O
O
H
CO2Me
H
O

16

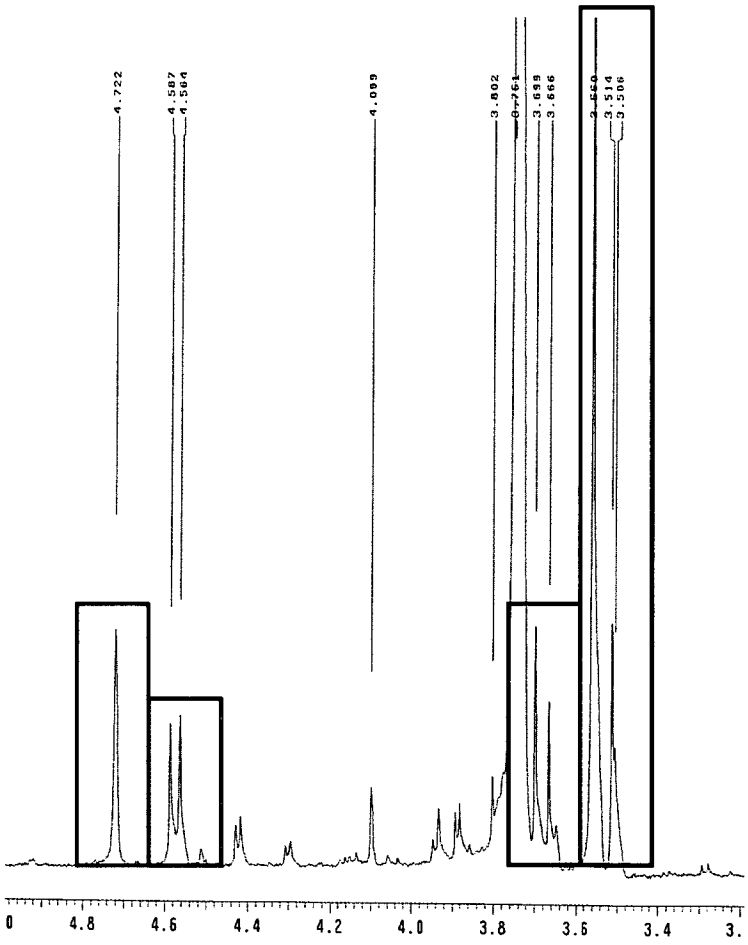

4.722
4.587
4.584
4.099
3.802
3.761
3.699
3.666
3.550
3.514
3.506
0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.

Figure 8(B)

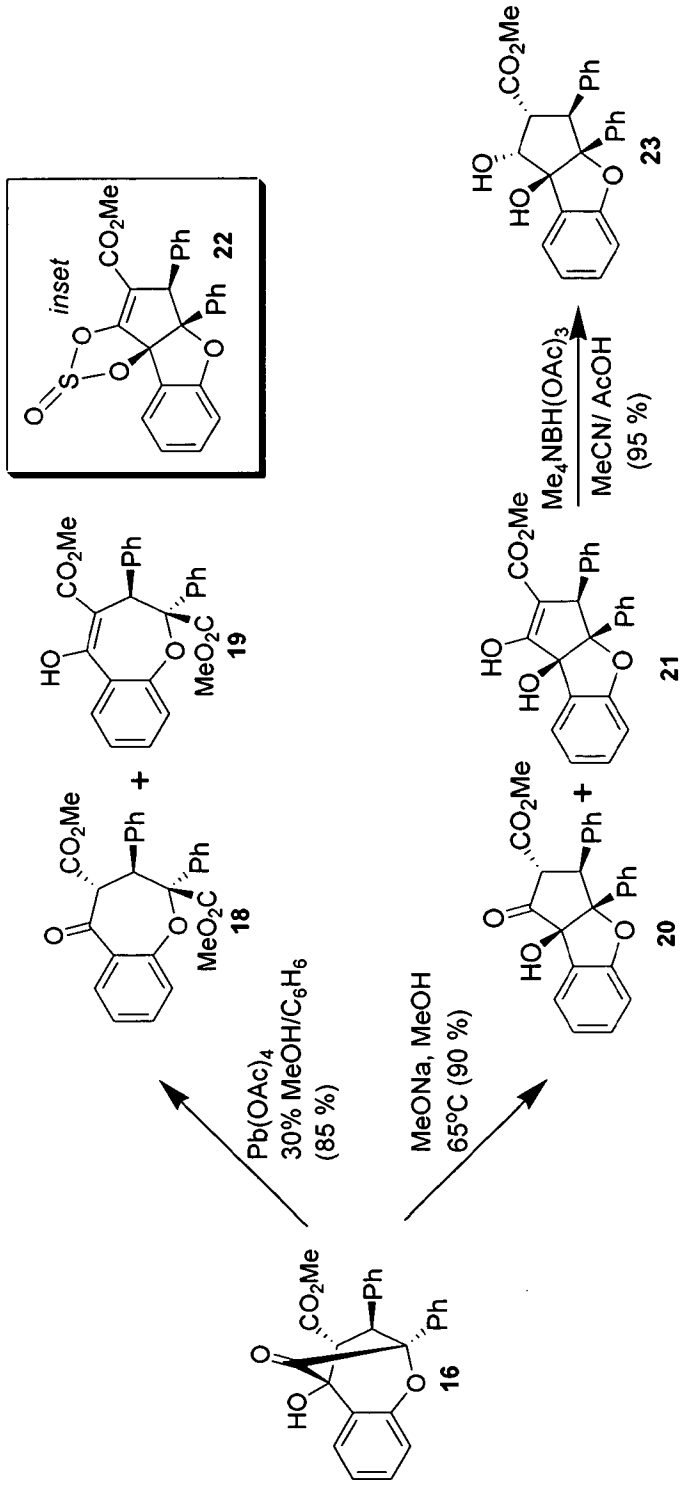

inset
22
19
18
16
21
20
23
Pb(OAc)4
30% MeOH/C6H6
(85 %)
MeONa, MeOH
65°C (90 %)
Me4NBH(OAc)3
MeCN/ AcOH
(95 %)

Figure 9

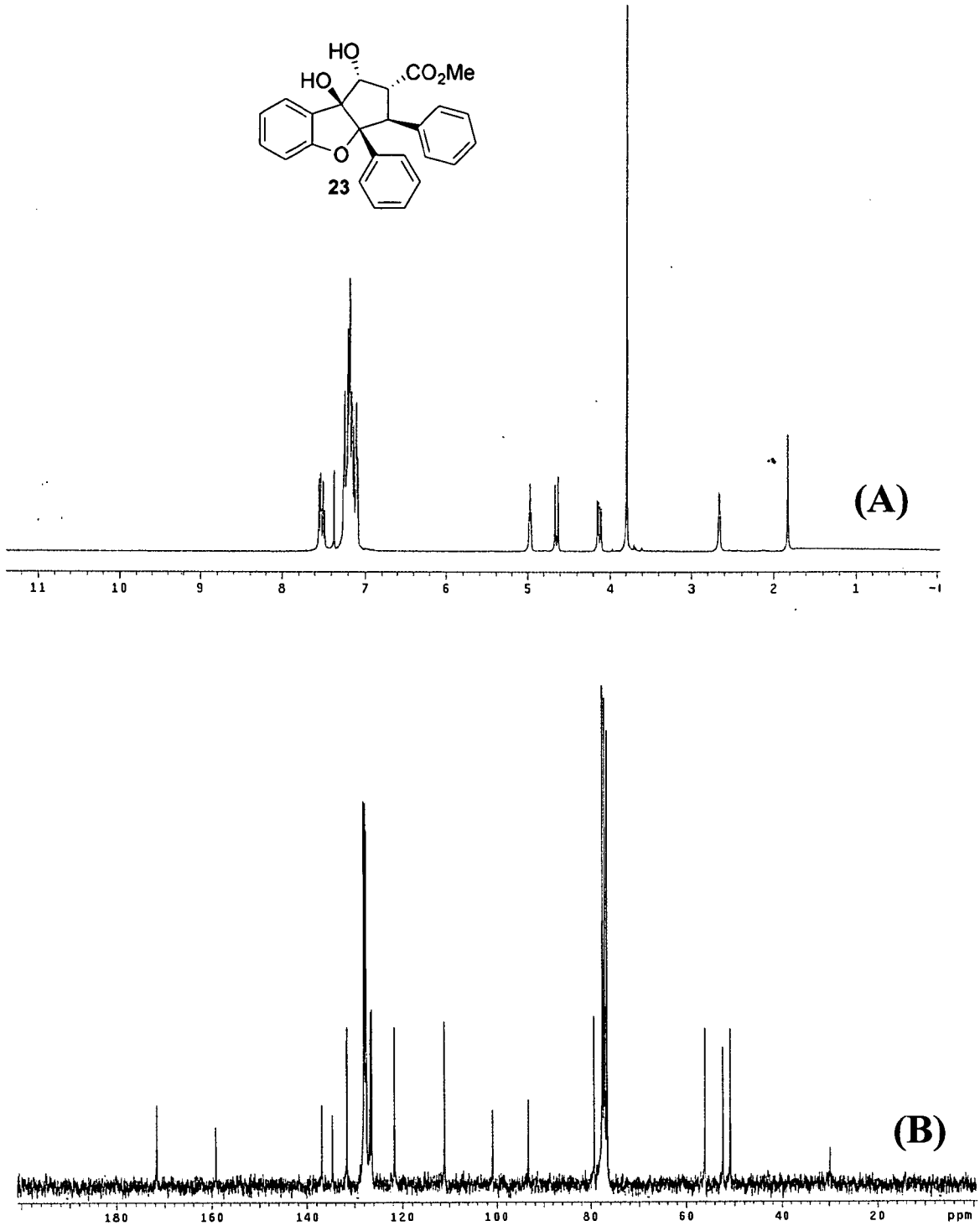

HO
HO
CO2Me
O
23
(A)
11
10
9
8
7
6
5
4
3
2
1
(B)
180
160
140
120
100
80
60
40
20
ppm

Figure 10

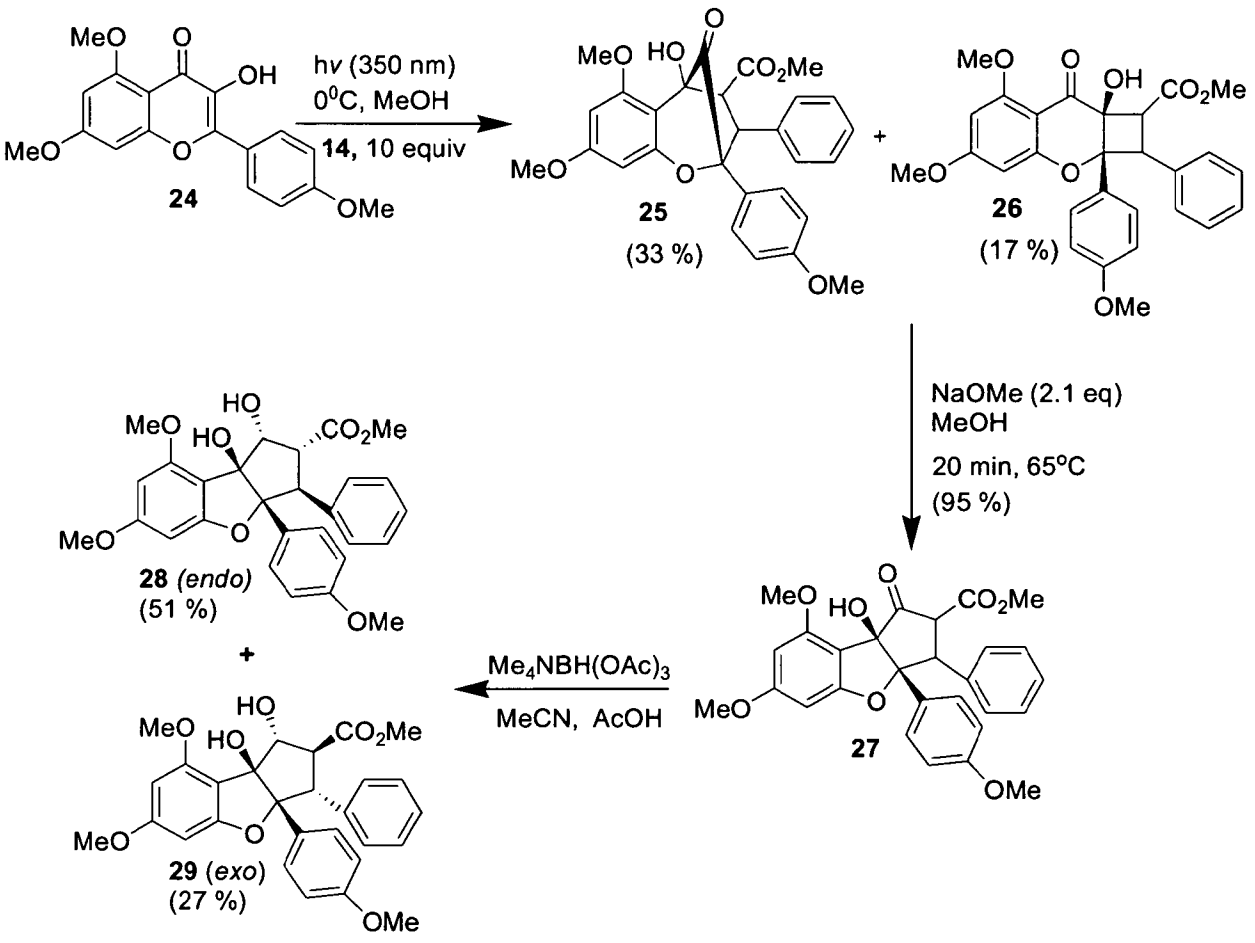

MeO
O
OH
MeO
O
24
OMe
hν (350 nm)
0°C, MeOH
14, 10 equiv
MeO
HO
O
CO2Me
MeO
O
25
(33 %)
OMe
+
MeO
O
OH
CO2Me
MeO
O
26
(17 %)
OMe
NaOMe (2.1 eq)
MeOH
20 min, 65°C
(95 %)
MeO
HO
O
CO2Me
MeO
O
27
OMe
Me4NBH(OAc)3
MeCN, AcOH
HO
MeO
HO
CO2Me
MeO
O
28 (endo)
(51 %)
OMe
+
HO
MeO
HO
CO2Me
MeO
O
29 (exo)
(27 %)
OMe

Figure 11

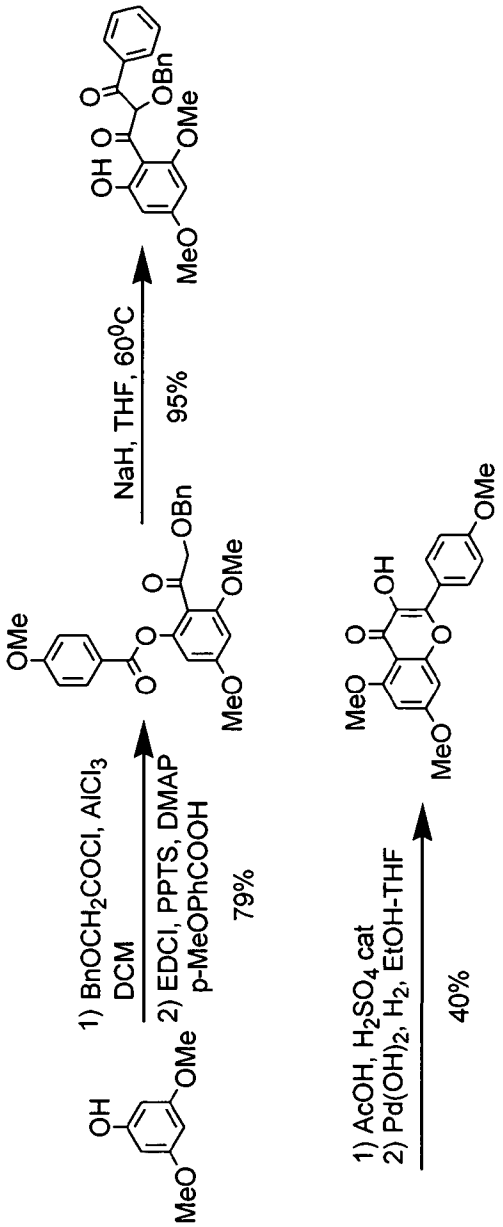
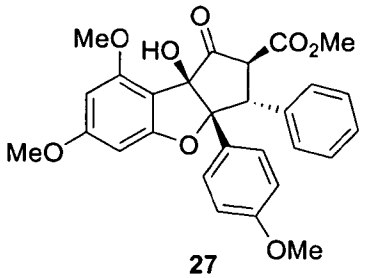
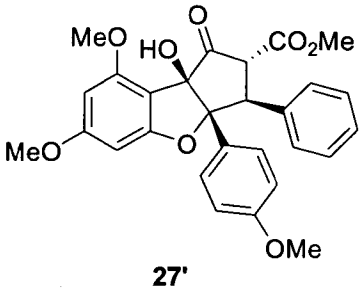

1) $BnOCH_2COCl$, $AlCl_3$
DCM
2) EDCI, PPTS, DMAP
p-MeOPhCOOH
79%
NaH, THF, 60°C
95%
1) AcOH, H_2SO_4 cat
2) $Pd(OH)_2$, H_2, EtOH-THF
40%
OH
OMe
MeO
OBn
O
OMe

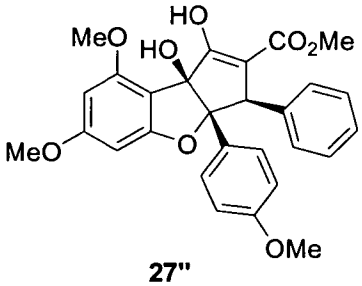
Figure 12



27



27'



27"

Figure 13

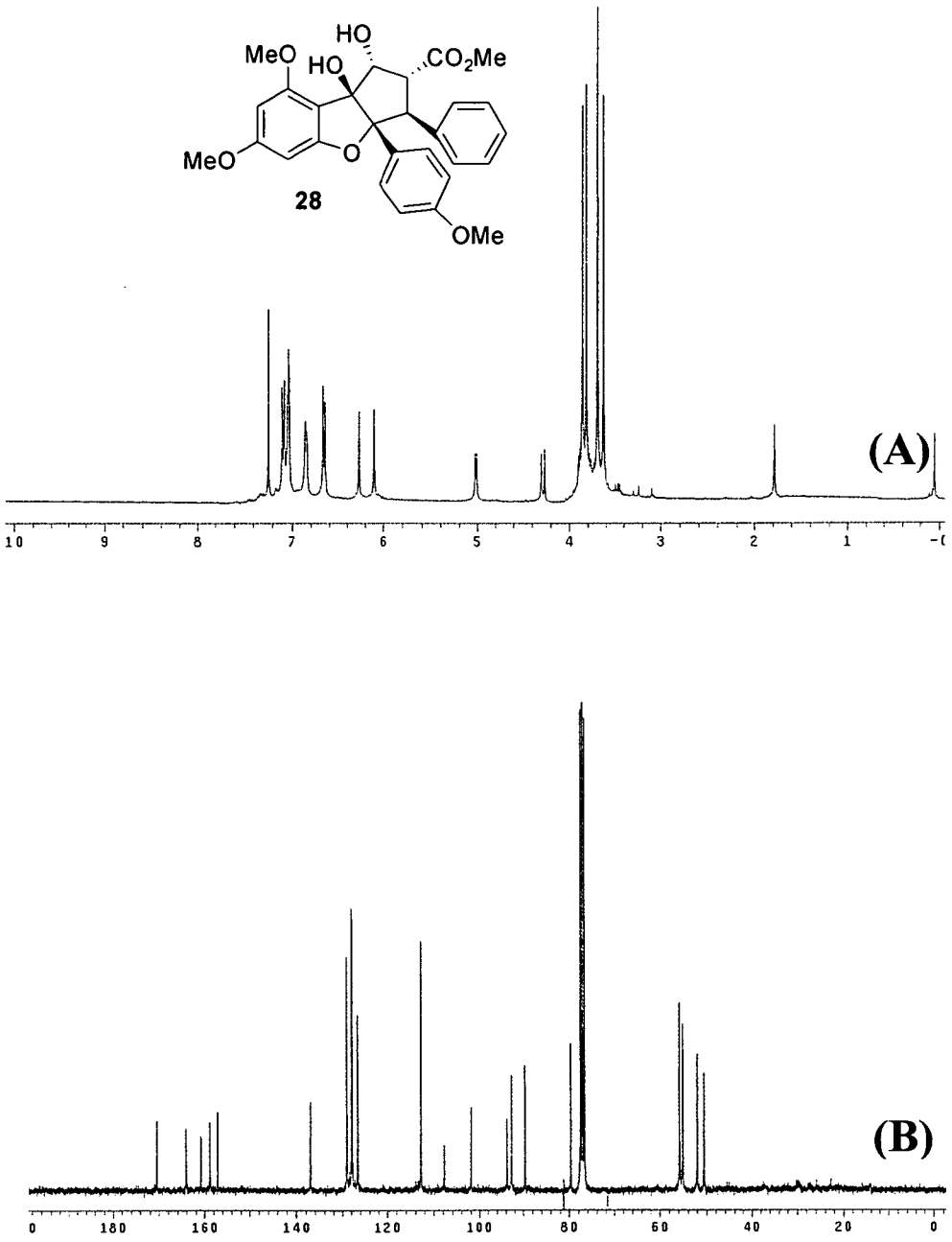

HO
MeO
HO
CO2Me
MeO
O
28
OMe
(A)
10
9
8
7
6
5
4
3
2
1
(B)
0
180
160
140
120
100
80
60
40
20
0

Figure 14

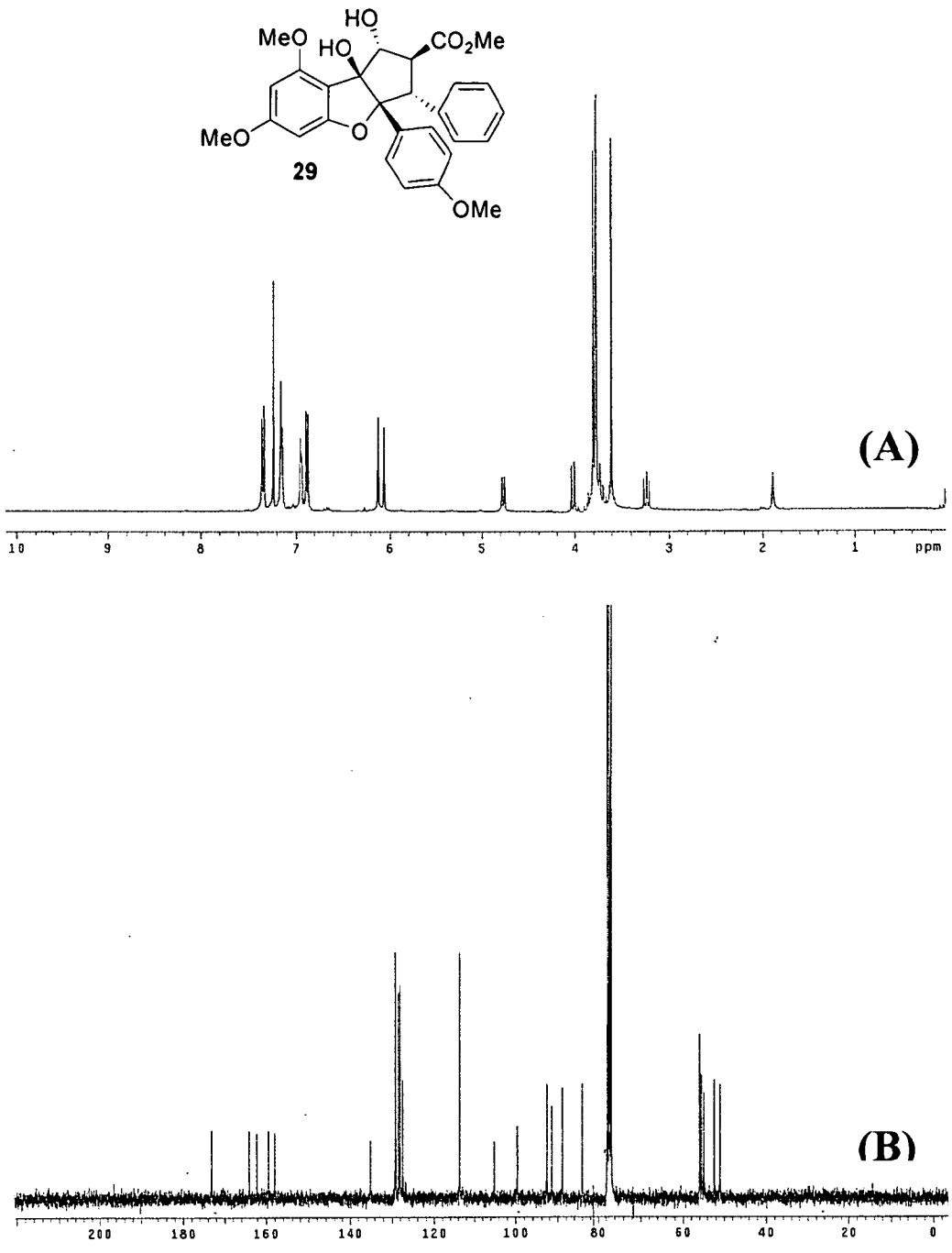

HO
MeO
HO
CO2Me
MeO
O
29
OMe
(A)
10
9
8
7
6
5
4
3
2
1
ppm
(B)
200
180
160
140
120
100
80
60
40
20
0

Figure 15

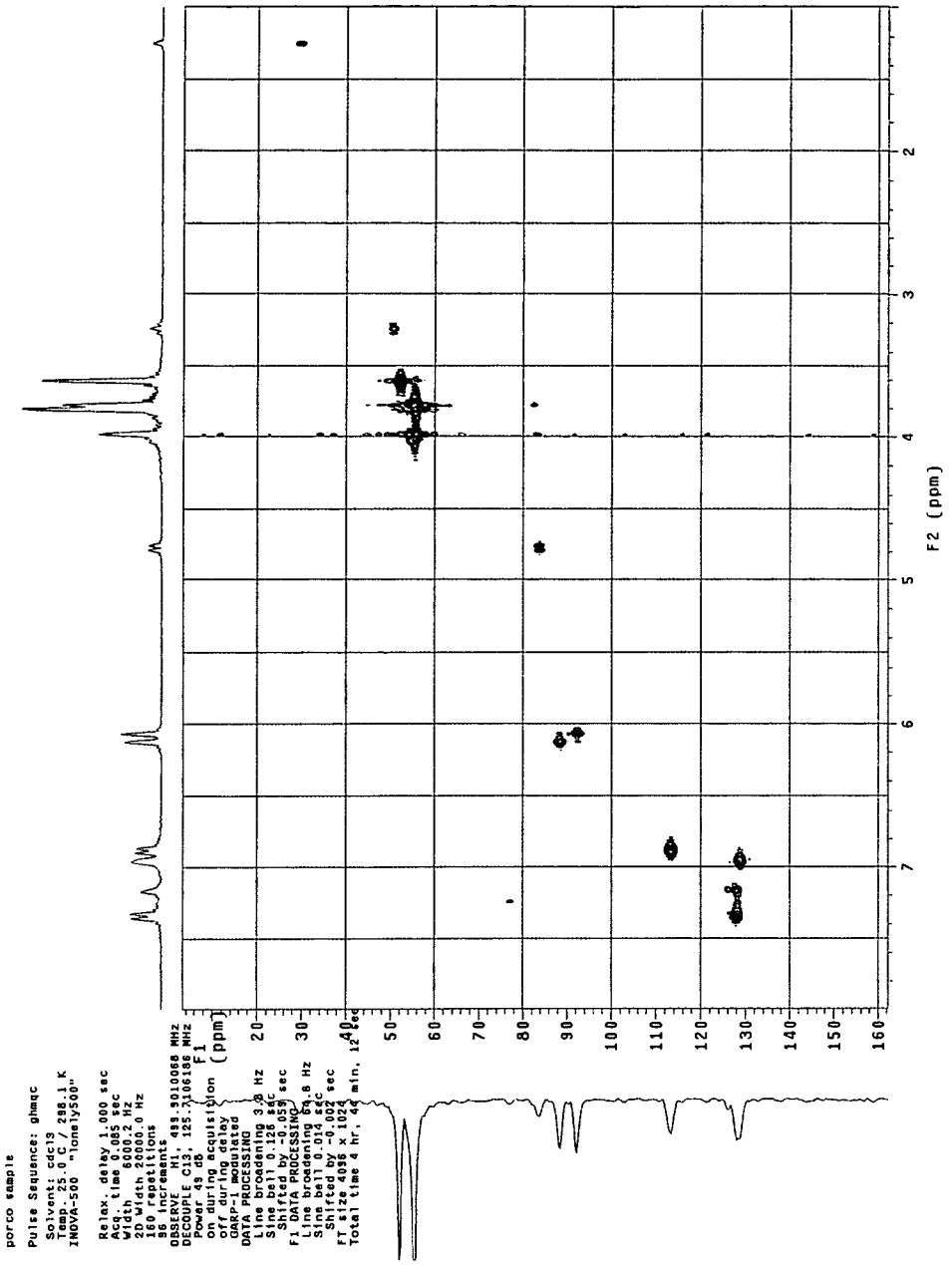

porco sample
Pulse Sequence: ghmqc
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
INOVA-500 "tonely500"
Relax. delay 1.000 sec
Acq. time 0.085 sec
Width 6000.2 Hz
2D Width 20000.0 Hz
160 repetitions
96 increments
OBSERVE H1, 499.3010068 MHz
DECOUPLE C13, 125.7106188 MHz
Power 49 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Line broadening 3.0 Hz
Sine bell 0.128 sec
Shifted by 0.059 sec
FT size 4096 x 1024
Total time 4 hr, 44 min, 12 sec
F1 (ppm)
F2 (ppm)

Figure 16

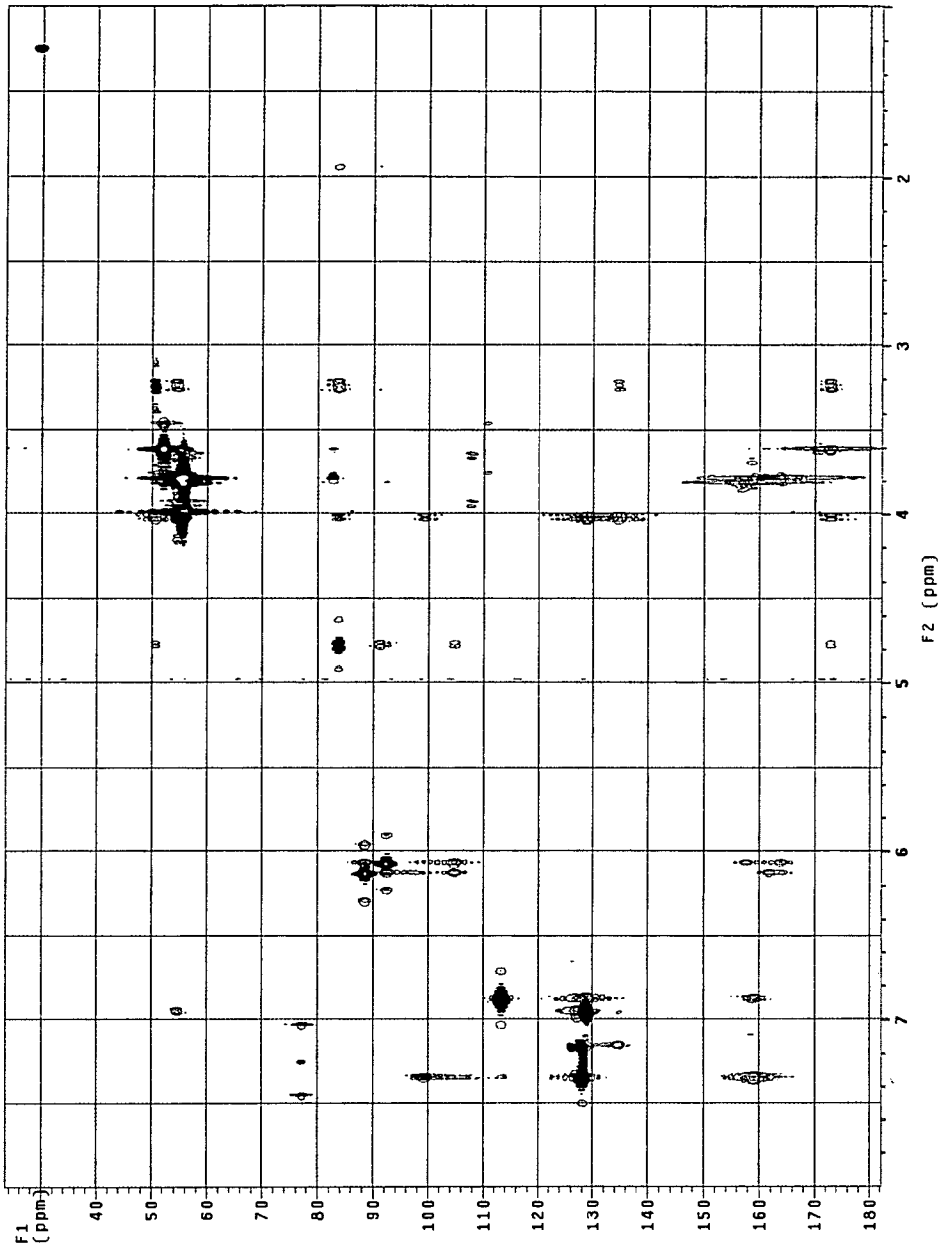
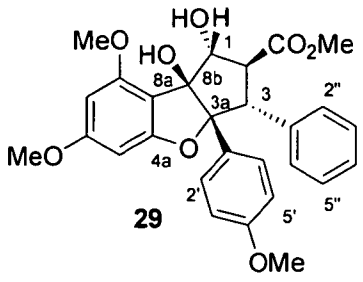

F2 (ppm)
F1 (ppm)
2
3
4
5
6
7
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

Figure 17


HOH
MeO
HO
1
CO2Me
8a
8b
3
2"
3a
MeO
4a
O
2'
5'
5"
OMe

29

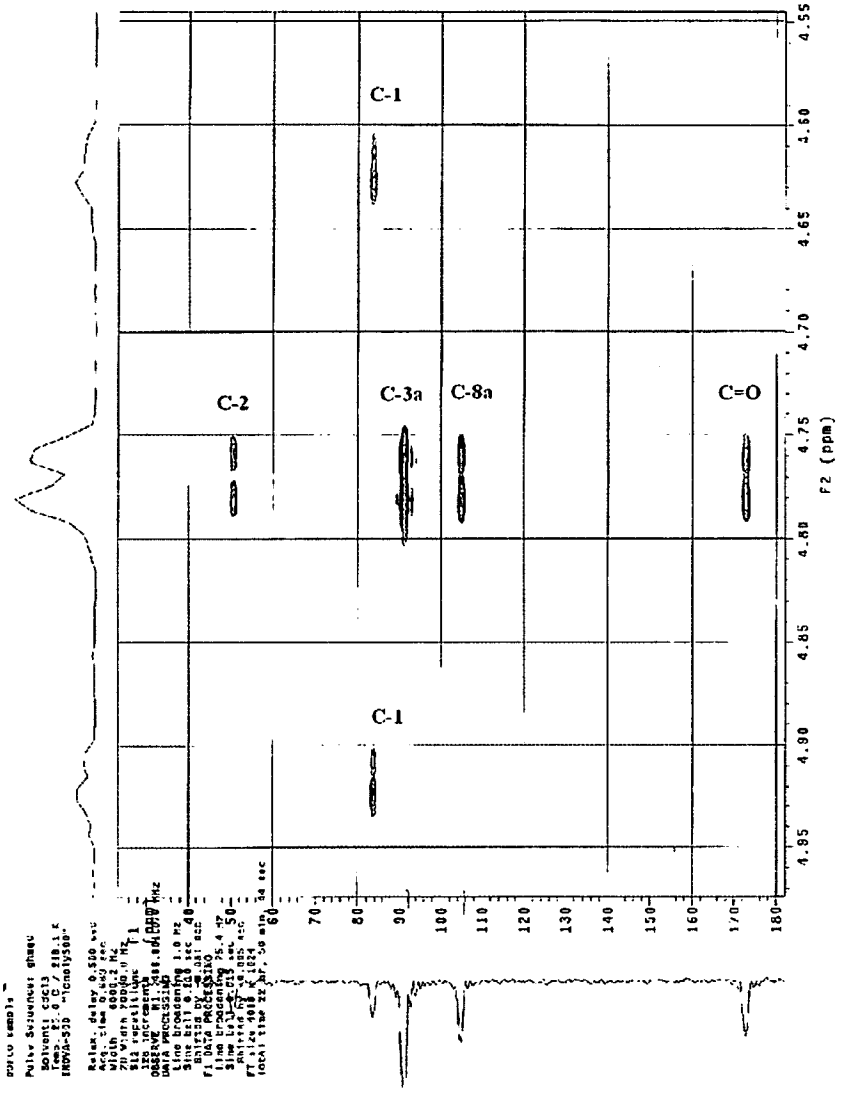

C-1
C-2
C-3a
C-8a
C=O
C-1
F2 (ppm)

Figure 18

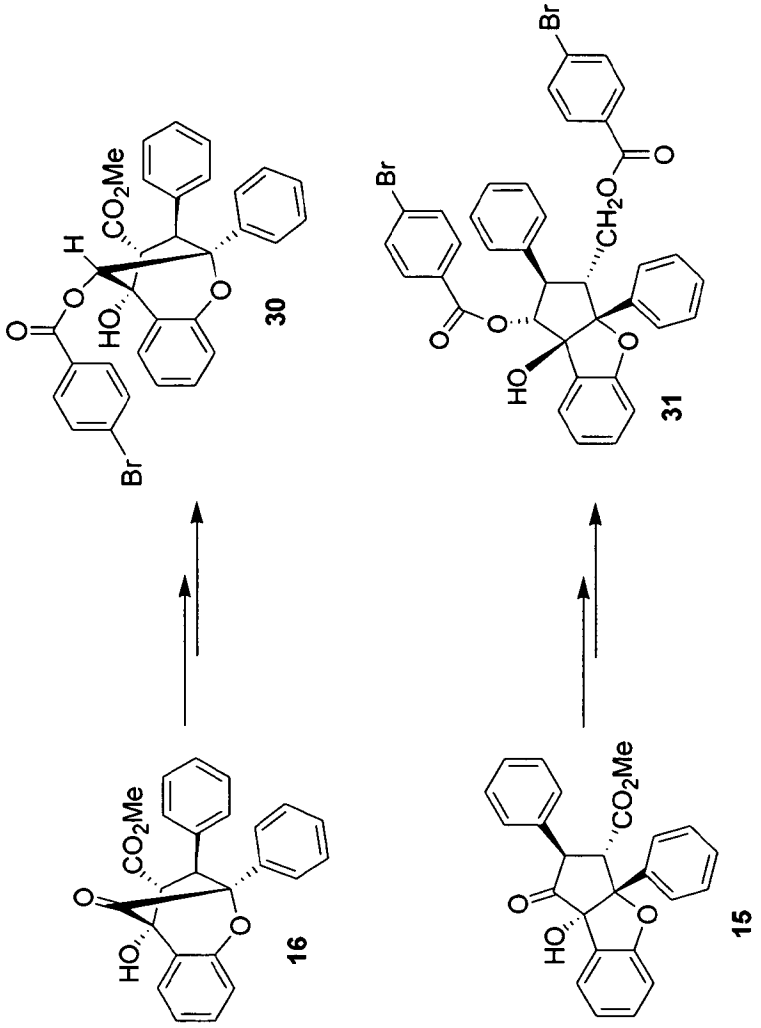


Figure 19

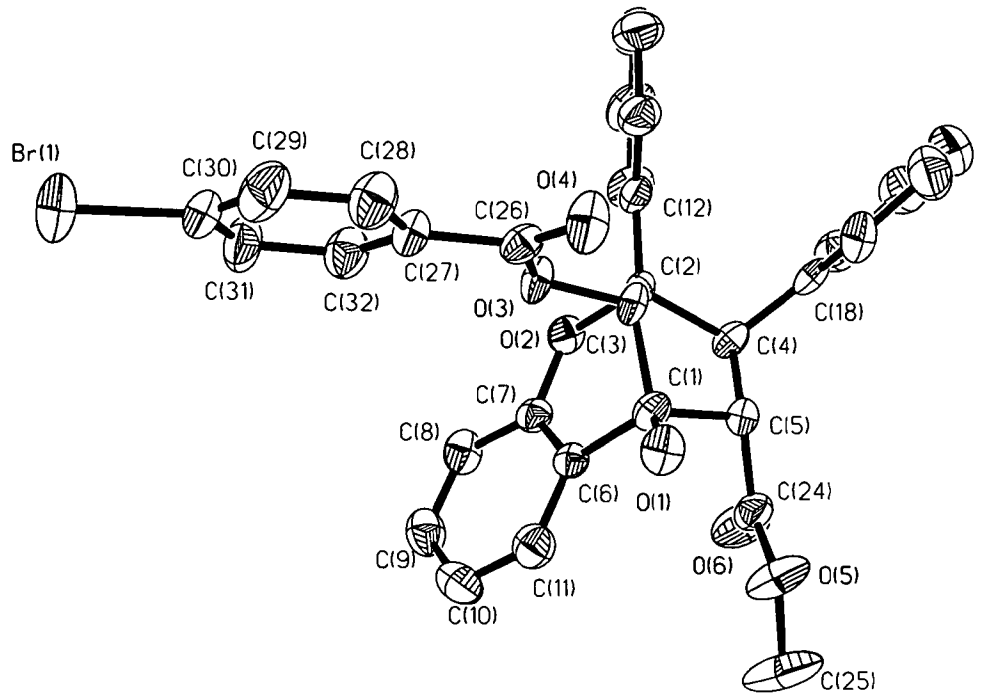

Br(1)
C(30)
C(29)
C(28)
C(31)
C(32)
C(27)
C(26)
O(4)
C(12)
C(2)
O(3)
O(2)
C(3)
C(4)
C(18)
C(7)
C(1)
C(8)
C(5)
C(6)
O(1)
C(24)
C(9)
O(6)
O(5)
C(11)
C(10)
C(25)

Figure 20

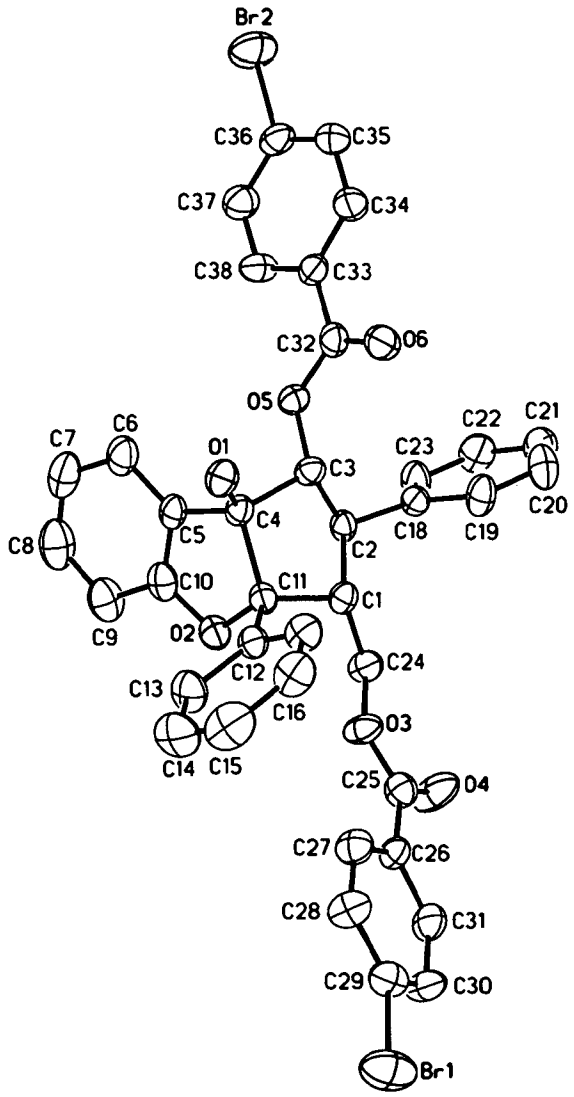

Br2
C36
C35
C37
C34
C38
C33
C32
O6
O5
C6
C7
O1
C3
C22
C21
C23
C20
C5
C4
C18
C19
C8
C2
C10
C11
C1
C9
O2
C12
C24
C13
C16
O3
C14
C15
C25
O4
C27
C26
C28
C31
C29
C30
Br1

Figure 21